HYPERHOMOCYSTEINEMIA IN ACUTE ISCHEMIC STROKE

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BONAFIDE CERTIFICATE

This is to certify that dissertation named **"HYPERHOMOCYSTEINEMIA IN ACUTE ISCHEMIC STROKE"** is a bonfide work performed by Dr.Kiran Josy Kanjamala , post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfillment of regulations of the Tamilnadu Dr. M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from 2013 to 2016.

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DECLARATION

I solemnly declare that this dissertation **"HYPERHOMOCYSTEINEMIA IN ACUTE ISCHEMIC STROKE"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Prof**.**Dr S.Mayilvahnnan M.D.**, Professor, Department of Internal Medicine,Government Royapettah Hospital, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

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CONTENTS

INTRODUCTION

Stroke remains a major cause of mortality and morbidity worldwide. The burden of stroke arises largely from the elderly population which may be due to fact that a wide range of risk factors are present in them.

There is growing evidence that high homocysteine levels contribute to the pathogenesis of ischemic stroke. Homocysteine is believed to cause atherogenesis and thrombogenesis via endothelial damage, vascular smooth muscle proliferation, and coagulation abnormalities. High homocysteine levels are associated with increased risk of cardiovascular and cerebrovascular disease.Although there are studies that show no increase in risk, there is still debate as to the strength and validity of the association. This disparity may be partly explained by methodological differences between the different studies, such as use of fasting and non-fasting samples, differing timing of sampling post-stroke and different subtypes of strokes studied.

There is a lot of research in the field of stroke in young and it's various etiologies. Various studies are currently assessing the role of homocysteine as a independent risk factor in stroke in ischemic stroke patients and its possible implication in prevention. This study will correlate the serum homocysteine level in patients with ischemic stroke.

AIM OF THE STUDY

TO STUDY THE LEVEL OF HOMOCYSTEINE IN ACUTE ISCHEMIC STROKE AND TO FIND THE CORRELATION BETWEEN HYPERHOMOCYSTEINEMIA AND ACUTE ISCHEMIC STROKE

REVIEW OF LITERATURE

Stroke is one of the major cause of mortality and morbidity worldwide, with ischemic stroke being the predominant type all over the world. With the current ageing population, ischemic stroke burden will inevitably increase leading to increasing demand for more effective prevention, diagnosis, and treatment strategies.About 15 million people are affected by stroke worldwide and out of this one thirds die and one thirds are left permanently disabled. Stroke is defined as "rapidly developed signs of focal or global disturbance of cerebral function lasting longer than 24 hours(if not interrupted by death) with no apparent non-vascular cause" by the WHO[3].

DEFINITION OF ISCHEMIC STROKE SUBTYPES

There are two commonly used classification systems for ischemic stroke.

1)THE OXFORDSHIRE COMMUNITY STROKE PROJECT

2)THE TRIAL OF ACUTE STROKE TREATMENT

CLASSIFICATION SYSTEMS.

[18]OXFORDSHIRE COMMUNITY STROKE PROJECT CLASSIFICATION

The OCSP classification categorized ischemic stroke according to clinical presentation into four subtypes based on initial symptoms, providing an estimation of magnitude and location of cerebral infarct:

1.total anterior circulation infarct

2.partial anterior circulation infarct

3.posterior circulation infarct

4. lacunar infarct

[19]TRIAL OF ACUTE STROKE TREATMENT CLASSIFICATION

The TOAST classification categorized ischemic stroke according to pathology into five subtypes based on clinical symptoms, neuroimaging data, and other diagnostic tests

1.large-vessel disease – large extra-cranial or intra-cranial artery stenosis usually of atherosclerotic nature

2. small-vessel disease – equivalent to a lacunar infarct within the white matter and deep grey matter in the brain

3.cardioembolic stroke–arterial thrombus or embolus of cardiac

origin

4.stroke of other determined etiology

5.stroke of undetermined etiology – there are two possible causes,

a)no identified causes

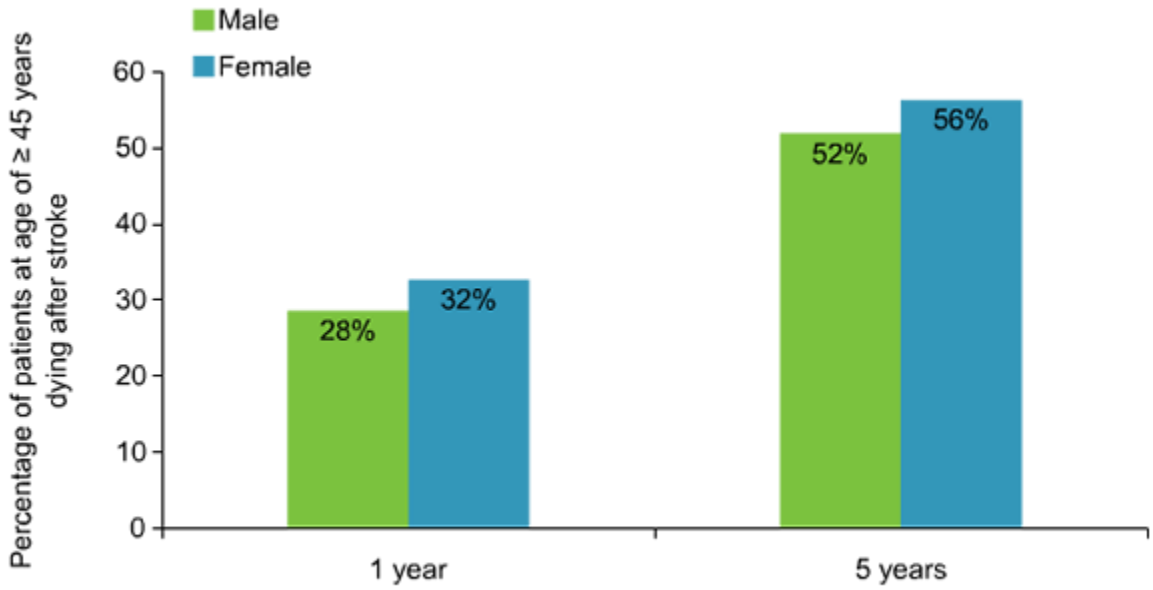
b) incomplete investigation.

EPIDEMIOLOGY

Statistics from all over the world shows that 14 million people suffer a stroke every year out of which 1/3 die and 1/3 are left permanently disabled[1].

In India, prevalence rate of stroke range from 84-262/100,000 in rural and 334-424/100,000 in urban areas. The incidence rate is 119-145/100,000 based on the recent population based studies. There is also a wide variation in case fatality rates with the highest being 42% in Kolkata among the stroke registries in Kolkata, Bangalore, Mumbai and Trivandrum[1].

Mortality following a stroke[17]



RISK FACTORS

Modifiable risk factors

The modifiable risk factors are high blood pressure, diabetes mellitus, cardiac diseases(such as AF, heart failure, and MI), high cholesterols, cigarette smoking, alcohol consumption, obesity, sedentary lifestyle, and unhealthy dietary habits

Increased blood pressure contributes greatly to stroke and its proper management lead to a significant reduction of stroke incidence and recurrence[22]. This is very much seen with cigarette smoking also.

High total cholesterol and low-density lipoprotein and low high-density lipoprotein

had been associated with increased risk of myocardial infarction but this increased risk is more modest among ischemic stroke. Beneficial effect is seen with moderate consumption of alcohol. However, high alcohol consumption has the opposite association and is a risk factor, possibly acting through elevation of blood pressure and subsequently cardiac diseases. High salt intake and lack of physical activity also contribute towards stroke risk. Moderate- to heavy-intensity physical activity had been shown to have protective effect against ischemic stroke.

Non-modifiable risk factors

Age, gender, ethnicity are non-modifiable risk factors. Age is the strongest risk factor for stroke; stroke risk has an approximately two-fold increase with every increasing decade after the age of 55 years[4]. Men have a higher stroke incidence and mortality compared to women.However, with the considerable elevation of stroke rates in older age group, more women are suffering from this condition as women tend to live longer[4]. Different ethnic groups have shown different stroke incidence and different stroke subtypes. Asians, African Americans and Hispanic Americans are shown to have higher incidence compared to the Caucasians[20]. Intracranial atherosclerosis is more prevalent among the Asians, Africans Americans, and Hispanics Americans, while extra cranial carotid stenosis is most common among Caucasians. Genetic predisposition to stroke had been demonstrated in family history and twin studies, and this is especially prominent

among younger individuals[21].

Other risk factors

Inflammation, infection, hypercoaguable states, usage of hormone replacement therapy and oral contraceptives, and socioeconomic factors are some of the potential risk factors that have been been associated with ischemic stroke.

EVALUATION OF STROKE[4]

When a stroke patient is brought to the casualty,the ABC s of the patient should be stabilized ie the airways ,breathing and the circulation should be taken care of which is followed by a quick neurological assessment of the patient
and the associated comorbidities present in the patient.When a patient presents with ischemic stroke like symptoms,we should first rule out other common conditions such as hypoglycaemia ,seizures ,hypertensive encephalopathy and other stroke like conditions, since these conditions can be easily treated.

FEATURES OF CLINICAL CONDITIONS MIMICKING STROKE[2]

1.Seizures - seizures noted, witness history, postictal state

2.Hypoglycaemia – h/o diabetes,low blood glucose,altered sensorium

3.Complicated migraine- h/o preceding aura, u/l headache

4.CNS abscess – headache,fever,endocarditis

5.CNS tumour- headache,slow progression,primary at another place

6.Drug intake- lithium,phenytoin

7.Psychogenic- inconsistent examination findings

8.Wernickes encephalopathy - c/c alcoholism,ataxia,confusion

9.Hypertensive encephalopathy- uncontrolled hypertension, headache, seizure, cerebral oedema

PATIENT HISTORY

It is very important to ascertain the time of onset of the stroke symptoms from the patient since this is most important piece of history on which further treatment and management of the patient depends.

The time of onset of stroke is made out as when the patient was at his or her previous baseline or symptom-free phase. For patients who are unable to provide this information such as patients who suffered a stroke during their sleep or who was found unconscious somewhere the time of onset of stroke is taken as when the patient was last known to be awake and symptom-free or known to be normal.

[4]The symptoms that one should carefully ask for in a case of ischemic stroke are

1.sudden weakness

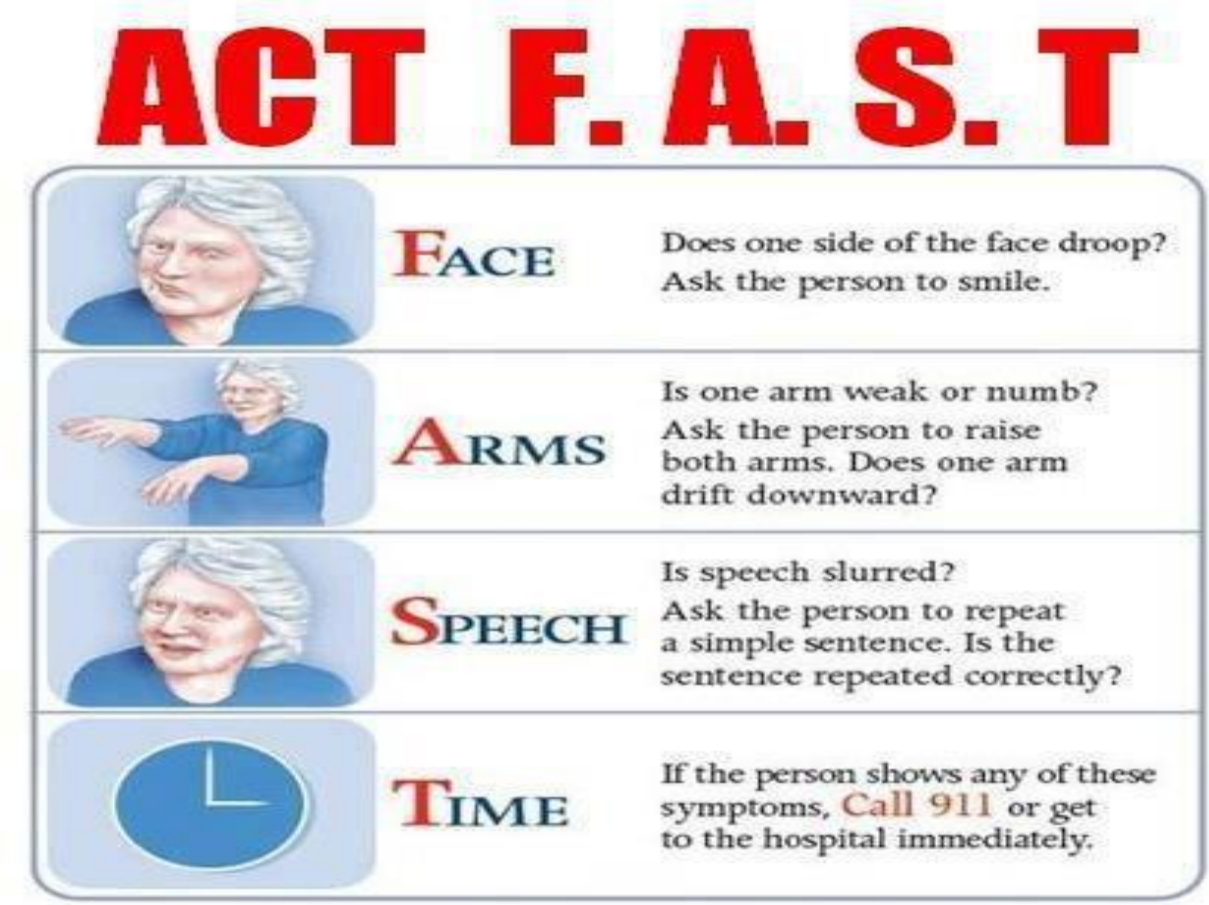
2.sudden speech disturbances

3.sudden visual loss

4.sudden dizziness

4.sudden,severe headache .

The FAST ie face, arm, speech, time protocol is being followed now.



GENERAL EXAMINATION

On admission, a complete physical examination is carried out on the patient by a physician or a neurophysician and a complete neurological workup and examination is done. Initially like all patients received in the casualty, the patients airway ,breathing and circulation should be checked and the vitals such as heart rate, blood pressure, temperature and oxygen saturation should be carefully assessed and stabilized.

The main goal of general examination is to identify the cause of stroke in the patient and to assess the signs and symptoms in the patient in relation to the stroke such as presence of any signs of trauma on the head or a tongue bite in relation to a seizure,carotid bruit, any cardiac murmurs,arrhythmias or look for any signs of coagulopathy or emboli such as Osler nodes or Janeway lesions.

[4]IMMEDIATE DIAGNOSTIC STUDIES TO BE DONE IN A CASE OF ACUTE ISCHEMIC STROKE

ALL PATIENTS

1.CT OR MRI BRAIN

2.RANDOM BLOOD SUGAR

3.CBC

4.RENAL FUNCTION TESTS

5.SERUM ELECTROLYTES

6. SP O2 STATUS

7.ELECTROCARDIOGRAM

8.PT/APTT/INR

IN SELECTED PATIENTS

1.LIVER FUNCTION TESTS

2.PREGNANCY TESTS

3.BLOOD ALCOHOL LEVEL

4.ABG ANALYSIS

5.TOXICOCLOGY SCREEN

6.CHEST XRAY

7.EEG (IF SUSPECTING ASSOCIATED SEIZURES)

8.LUMBAR PUNCTURE(IF SAH IS SUSPECTED

9.TT TIME IF THE PATIENT IS TAKING DIRECT THROMBIN OR DIRECT FACTOR Xa INHIBITORS

GENERAL SUPPORTIVE CARE

Airway and Ventilatory Support

In a patient with ischemic stroke,there is a chance of decreased tissue oxygenation and energy supply to the periphery due to the concomitant presence of hypoxemia and hypotension and, if present,it should be always be corrected to limit further damage at a cellular level.Hence a constant reassessment of the ABCs of the patient is required.

Hypoxia[23]

Hypoxia is a very frequent finding after stroke and usually a stroke patient, develops hypoxia within 48 hours of stroke onset. Common causes of hyoxia in a stroke patient include obstruction of the airways,decreased work of breathing and aspiration due to loss of consciousness and associated pneumonia due to secondary infections.Since there is an loss of oropharyngeal mobility and upper airway

protective reflexes in the unconscious,they are at an increased risk to develop respiratory complications.When the oxygen saturation falls to dangerously low levels, the patients develop Cheyne-Stokes respiration[central periodic breathing].

Patient Positioning[24]

The position of the patient is of utmost importance since it can affect the oxygen saturation,the cerebral perfusion pressure, the MCA mean flow velocity, and intracranial pressure.The supine position is the best for stroke patients as it has a very minute effect on oxygen saturation and also increases the perfusion of he cerebral vessels.The head end of the patient should be elevated to about 15 to 30 degrees to prevent any aspiration and also in those suspected to have increased intracranial pressure.

Oxygen Maintenance[24]

In a patient with ischemic stroke, there may be a gradual improvement of the neurological defecits if oxygen is started within 12 hours of onset.The oxygen saturation of the patient should be maintained above 94% and oxygen can be given via a nasal cannula or a Venturi mask. If the patient is haemodynamically unstable then oxygenation is done via continuous positive airway pressure, or endotracheal intubation with mechanical ventilation which can decrease intracranial pressure or brain edema if present.

Temperature[25]

Hyperthermia

Hyperthermia in stroke patients usually indicate a secondary infection such as pneumonia or urinary tract infection or an ongoing sepsis or could be due to a pontine stroke.It is usually present in more than one – third of stroke patients and if present it usually denotes a poor neurological outcome due to increased production of free radicals or increased release of neuro transmitters and any hyperthermia in stroke patients should be immediately investigated and treated accordingly.Antipyretics are useful to reduce the temperature in such cases and aspirin also has a thermoregulatory action and helps in achieving the normal temperature.

Heart monitoring

Stroke patients have a very high probability of sustaining a number of cardiac arrythmias and hence it would be ideal that they undergo continuous cardiac monitoring from the time of admission up until 24 hours after stroke. This will help in the detection of any atrial fibrillation, supraventricular tachycardias or any other arrythmias during stroke and can be accordingly treated.

Blood Pressure

Hypertension

Arterial blood pressure varies significantly in stroke patients and it can have significant clinical consequences.Usually all ischemic stroke patients have an increased blood pressure if the stroke patient had hypertension before the onset of stroke then the blood pressure will be much higher compared to an a patient who didn't have hypertension before stroke.After that the blood pressure starts decreasing in about 1 and half hour after stroke.Very high blood pressure is highly detrimental to the patient as it can lead to hypertensive encephalopathy, multiple arrhythmias and renal failure. It can also increase the already present cerebral edema or can lead to the hemorrhagic transformation of the infarcted tissue.Very high blood pressure can also decrease the blood supply to the other major organs and also the brain exacerbating the ischemic insult. Slight increase in blood pressure is helpful for the patient since it help in increasing blood flow to the ischemic tissue.

[4]The blood pressure shouldn't be decreased during the initial period of stroke unless the blood pressure is >220/120 mm Hg or there is an associated medical disability,for example acute coronary syndrome, heart failure or aortic dissection that requires the blood pressure to be lowered drastically for the well being of the patient.In such conditions, the blood pressure should be lowered by 30% of the

mean arterial pressure or 15% of the systolic blood pressure and during this reduction the patient should be checked for any neurological deterioration.If fibrinolytic therapy is to be started for the patient,then the blood pressure should be brought down to 185/110.The blood pressure should be maintained at this level or below during and after fibrinolysis to decrease the risk of intracranial haemorrhage in the patient.

[4]BLOOD PRESSURE CONTROL BEFORE THROMBOLYSIS

If BP is less than 185/110,the patient can be taken up for reperfusion therapy and if BP is above 185/110,then administer,

1. LABETALOL at the rate of 10-120 mg iv over one to two minutes ,and if recquired repeat once more
2. Next NICARDIPINE can be tried, about 5mg/hr infusion and can be titrated upto to a maximum of 15mg/hr by titrating by 2.5mg/hr every 15 minutes and then adjust to maintain the blood pressure
3. Other agent which can be used to decrease the blood pressure are hydralazine,enalaprilat etc.
4. If the blood pressure is not maintained below 185/110 ,rtPA should not be administered.

[5]MANAGEMENT OF BLOOD PRESSURE DURING AND AFTER REPERFUSION THERAPY

1.The blood pressure should be checked every fifteen minutes from the start of the infusion for a period of two hours,then every 30 minutes for the next six hours and then every hour for sixteen hours.

2.If the systolic blood pressure is greater than 180-230 or the diastolic blood pressure is greater than 105 – 120 , the following drugs can be used

a) Labetalol 10 mg iv loading dose followed by continuous infusion at the rate of 2 – 8 mg/min.

b)Nicardipine , about 5mg/hr infusion and can be titrated upto to a maximum of 15mg/hr by titrating by 2.5mg/hr every 5 - 15 minutes

c)Finally if the bood pressure is not controlled ,iv sodium nitroprusside can be tried.

Hypotension[26]

A patient with acute ischemic stroke episode is usually never hypotensive but if hypotension is present, then any associated comorbidities such as acute myocardial infarction , aortic dissection or shock should be present.The brain vulnerable to any hypotensive episodes since there is impaired cerebral autoregulation during acute ischemic stroke. Arterial hypotension on admission in acute ischemic stroke patients is associated with poor outcomes.The associated comorbidities should be

urgently treated so as to reduce the extent of brain damage due to hypotension.Ideally intravenous fluid should be used to correct the hypotension but if resistant to treatment,the vasopressor agents such as dopamine and noradrenaline should be tried next.

Intravenous Fluids[27]

Patients who had suffered an acute ischemic stroke episode are either hypovolemic or euvolemic.Hypovolemia is highly detrimental to the patient as it can decrease the perfusion of the brain and increase the area of infarct, lead to further thrombosis and can also lead to other major organ damage such as renal insufficiency. At the other end of the spectrum ,hypervolemia can increase the brain oedema and also increase the stress on the myocardium.Thus an euvolemic status should be always attained in an ischemic stroke patient. [4]For patients who present with euvolemia, maintenance intravenous fluids should be initiated which is calculated to be about 30 mL/kg of body weight.For stroke patients who are hypovolemic,there should be rapid replacement of the intravascular volume followed by maintenance intravenous fluids therapy and extra precaution is to be taken in those who are susceptible to intravascular volume overload, such as those patients with renal or cardiac failure.

If hypotonic solutions such as 5% dextrose or 0.45% saline is instituted to the patient,it is redistributed to the intracellular spaces which in turn can exacerbate

the brain edema and therefore isotonic solutions such as 0.9% saline which is distributed only into the extracellular spaces should be used for patients with acute ischemic stroke.

Blood Glucose

Hypoglycemia

If a stroke patient is found to be hypoglycaemic it may be due to a prolonged fasting state or if the patient was on anti diabetic medications.If hypoglycemia is severe, it will cause both autonomic and neurological symptoms, which are readily reversible if it is treated rapidly. However, severe or prolonged hypoglycemia can result in irreversible brain damage and the low levels should be treated as soon as possible.In a healthy individual,autonomic symptoms ie sweating trembling or anxiety appears in the patient when the blood glucose level falls below 57 mg/dL, and symptoms of brain dysfunction ie disorientation, slowing of speech or dizziness appears when the glucose level drops below 47 mg/dL[4] .However, in ischemic stroke patients with poorly controlled diabetes, these symptoms occur at higher blood glucose levels and in some cases brain dysfunction occurs before the autonomic symptoms. Hence it is of paramount importance that the hypoglycaemia is corrected as early as possible which is usually done by an intravenous push of 25 mL of 50% dextrose.

Hyperglycemia

Ischemic stroke patients who are diabetic are mostly found to have high blood sugar at the time of admission which may be due to a stress reaction and release

of catecholamines with impaired glucose metabolism.Ischemic stroke patients with hyperglycaemia are associated with a poor prognosis.The glucose levels of these patients should be maintained within the range of 140 to 180[4] with the help of subcutaneous insulin and further care should be taken that there is no over correction such that it can lead to hypoglycaemia.

Neurological Examination and Stroke Scale/Scores[6]

There are a number of stroke scales available which helps in the quantification of the neurological deficit and can also assess the prognosis of the stroke patients.The most commonly used ones is the National Institute Of Health Stroke Scale(NIHSS)

NATIONAL INSTITUTE OF HEALTH STROKE SCALE

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

ITEM	SCORE
Level of consciousness	
Alert	0 points
Drowsy	1 point
Stupor	2 points
Coma	3 points
Response to 2 questions (orientation)	
Know age and current month	0 points
Answers 1 question correctly	1 point
Cannot answer either question correctly	2 points
Response to 2 commands	
Follows 2 commands correctly	0 points
Follows 1 command	1 point
Cannot follow either command	2 points
Best gaze (movement of eyes to left or right)	
Normal eye movements	0 points
Partial gaze paresis to one side	1 point
Forced gaze palsy to one side	2 points
Visual fields	
No visual loss	0 points
Partial homonymous hemianopia	1 point
Complete homonymous hemianopia	2 points
Bilateral visual loss	3 points
Facial motor function	
No facial weakness	0 points
Minor unilateral facial weakness	1 point
Partial unilateral facial weakness	2 points
Complete paralysis of 1 or both sides	3 points
Upper-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of upper extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Lower-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of lower extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Limb ataxia (cannot be tested in presence of paresis)	
No limb ataxia	0 points
Ataxia present in 1 limb	1 point
Ataxia present in 2 limbs	2 points
Sensory function	
No sensory loss	0 points
Mild-to-moderate sensory loss	1 point
Severe-to-total sensory loss	2 points
Language	
Normal language	0 points
Mild-to-moderate aphasia	1 point
Severe aphasia	2 points
Mute	3 points
Articulation	
Normal articulation	0 points
Mild-to-moderate dysarthria	1 point
Severe dysarthria	2 points
Extinction or inattention (neglect)	
No neglect or extinction	0 points
Visual or sensory inattention or extinction	1 point
Profound inattention to visual and sensation	2 points

SOME SELECTED STROKE SCORING SYSTEMS[7]

Table Selected scores to predict outcome after ischemic stroke

Score	End point	Components	Risk assessment
Stroke-TPI[2]	Functional outcome after thrombolysis	Age, sex, DM, NIHSS score, previous stroke, SBP, OTT	Logistic regression equations
iScore[3]	Functional outcome in hospitalized stroke patients	Age, sex, smoking, preadmission dependency, AF, CHF, previous MI, cancer, renal failure on dialysis, glucose at presentation, stroke severity,[a] stroke subtype	5 risk categories by quintiles of risk score
DRAGON[4]	Functional outcome after thrombolysis	Age, prestroke mRS score, HDMCA sign or early infarction on CT, glucose at presentation, NIHSS score, OTT	Increasing risk of poor outcome for scores 0-10
SPAN-100[1]	Functional outcome after thrombolysis	Age + NIHSS score	Cutoff at 100
ASTRAL[5]	Functional outcome of stroke patients evaluated in the ED	Age, NIHSS score, time from onset to admission, LOC, range of visual fields, glucose at presentation	Integer-based point-scoring system
Postthrombolysis Risk Score[6]	Risk of ICH after thrombolysis	Age >60 y, NIHSS score >10, glucose >8.325 mmol/L, platelets <150,000/mm^3	Increasing risk of ICH for scores 0-4
HAT[7]	Risk of ICH after thrombolysis	DM or glucose at presentation ≥200 mg/dL, NIHSS score, hypodensity on CT	Increasing risk of ICH for scores 0-5
SEDAN[8]	Risk of ICH after thrombolysis	Age, NIHSS score, HDMCA signs, early infarct signs on CT, glucose at presentation	Increasing risk of ICH for scores 0-6
SITS-ICH Risk Score[9]	Risk of ICH after thrombolysis	Age, body weight, history of HTN, use of aspirin/clopidogrel, NIHSS score, SBP, glucose at presentation, OTT	Increasing risk of ICH for scores 0-12

EARLY DIAGNOSIS – BRAIN AND VASCULAR IMAGING

In a stroke patient, time is precious and brain imaging should be immediate so as to not only diagnose and find the cause but also to institute timely reperfusion therapy.An early brain imaging helps to identify the location ,the size ,the vascular territory of the infarct ,the presence or absence of any haemorrhage and the presence of any brain oedema.Although there a number of imaging techniques available in this modern era,non–contrast-enhanced computed tomography (NECT) is the most widely used one and ample to diagnose

ischemic stroke and also to find out the indication and contraindication for fibrinolysis which allows patients with ischemic stroke to receive timely fibrinolytic therapy and CT should be ideally taken within 25 minutes of the patient's arrival to the casuality[4].

Parenchymal Brain Imaging

NECT and Contrast-Enhanced CT Scans of the Brain

CT brain can identify almost all cases of intracranial hemorrhage and can also find the presence of brain tumour and hence is useful to exclude the contraindications of fibrinolytic therapy.[4]A CT can be used to visualize the presence of any parenchymal damage within 3 hours but one of its disadvantage is that it is not sensitive enough to pick up any acute and small cortical or subcortical infarctions, especially those present in the posterior fossa.Despite these disadvantages, its widespread immediate availability,ease of interpretation, and speed of retrieval,makes CT the most commonly used imaging modality in acute ischemic stroke.

NECT can identify early signs of ischemic injury or arterial occlusion.The common signs of cerebral ischemia that are seen very early are[4]

a) **loss of gray-white differentiation**

b) loss of distinction of the basal ganglia nuclei (**lenticular obscuration**)

c) blending of the densities of the cortex and underlying white matter in the insula (**insular ribbon sign**) and over the convexities (**cortical ribbon sign**)

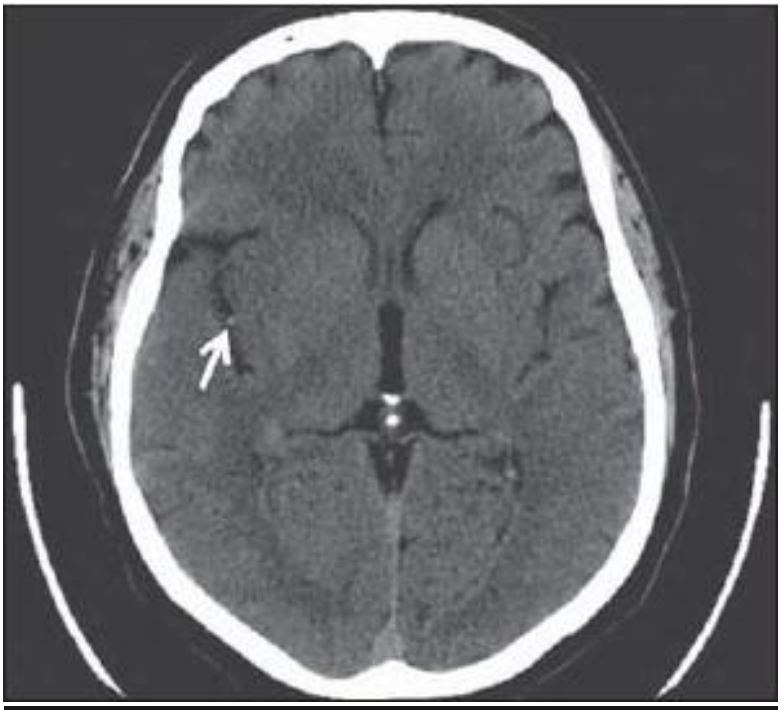
d) swelling of the gyri that produces **sulcal effacement**

e) increased density within the occluded artery ie **hyperdense middle cerebral artery (MCA) sign**, which is indicative of large-vessel occlusion

g) Hyperdense MCA "dot" sign is a clot within a branch of the MCA smaller than the thrombus volume in the MCA and hence a better target for intravenous fibrinolysis.

h) The **hyperdense basilar artery sign**.

DENSE MCA SIGN



HYPERDENSE MCA SIGN

LOSS OF INSULAR RIBBON

HYPERDENSE BASILAR ARTERY SIGN

MRI of the Brain

[4]Standard MRI sequences such as T1 weighted, T2 weighted, fluid-attenuated inversion recovery [FLAIR]) don't usually pick up the changes of acute ischemia. Diffusion-weighted imaging (DWI) is the most sensitive and specific imaging technique for acute infarct,much better than NECT or any other MRI sequence. DWI correctly identifies lesion size, site, and age. DWI can also pick up small cortical lesions and small deep or subcortical lesions, including those in the posterior fossa, areas which are poorly visualized with standard MRI sequences and NECT. DWI can identify satellite ischemic lesions that provide information on possible stroke mechanism.

The ***artery susceptibility sign*** is the magnetic resonance (MR) counterpart of hyperdense MCA seen on NECT[4].

Conventional MRI is more sensitive than NECT in identifying both new and preexisting ischemic lesions.DWI-positive lesions tend to be smaller and multiple in patients with TIA.

In the evaluation of acute stroke patient including identifying candidates for fibrinolytic treatment,MRI can be used as the sole imaging modality.Gradient MR echo sequences has the ability to detect silent prior microbleeds not picked up by NECT. These microbleeds represents markers of bleeding-prone angiopathy and may be associated with an increased risk of hemorrhagic transformation after antithrombotic and fibrinolytic therapy

The advantages of MRI compared with NECT for parenchymal imaging are[4]

1. Differentiating acute from chronic ischemia;
2. Identifying acute, small cortical, small deep, and posterior fossa infarcts;
3. Identification of subclinical satellite ischemic lesions
4. The avoidance of exposure to ionizing radiation
5. Greater spatial resolution.

Disadvantages of MRI are

1. Cost
2. Long duration of the test
3. Limited availability

4. Increased susceptibility to motion artifacts
5. Patient contraindications such as claustrophobia,cardiac pacemakers,or metal implants

Intracranial Vascular Imaging

Most of large strokes are caused by occlusion of more than one large vessel which are devastating hence detection of large-vessel occlusion by intracranial vascular imaging improves the ability to make just clinical decisions.Large-vessel occlusion can be identified by NECT.The length of clot within the middle cerebral artery is directly related to the success of recanalization with intravenous fibrinolysis.

CT Angiography

CT angiography (CTA) helps to assess the intra and extracranial vessels in acute, subacute, and chronic stroke and conveys information about the presence or absence of vessel occlusions or stenosis. The CTA is able to detect the stenosis and occlusions in the large vessels but is not able to detect the flow rates and direction of flow of blood which is provided by digital substraction angiography.CTA andMRI/DWI are comparable for detecting ischemic regions, with DWI better at bringing out smaller abnormalities and those in the brainstem and posterior fossa.In early strokes ie less than 3 hours, CTA accurately predicts the volume of tissue that will ultimately become infarcted which is not with the case with NECT.CTA gives an estimate of cerebral blood volume rather than the expression

of cytotoxic edema seen on NECT.

MR Angiography(MRA)

Intracranial MR angiography is performed along with brain MRI and helps in therapeutic decision making.

Conventional Angiography

Digital substraction angiography(DSA) is the "gold standard" imaging modality for many types of cerebrovascular lesions.The resolution, sensitivity, and specificity of DSA is higher than those of the noninvasive techniques, but DSA is an invasive test and can cause major complications such as stroke and death.Cerebral angiography should not be the initial imaging modality of choice for emergency evaluation of stroke because of the time necessary to perform the examination,a CTA or MRA can be done in an additional 2 to 4 minutes during initial stroke work up and can negate the need for catheter angiography.

Extracranial Vascular Imaging

The extracranial blood vessels should be screened to not only find out the cause of stroke but also to prevent recurrences. To find out the degree of stenosis and for determination of eligibility for CEA or carotid angioplasty and stenting, [4]DSA is the "gold standard" imaging modality.CTA and multimodal MRI are best for detecting dissection.A very high-grade stenosis ("**string sign**") is best detected by DSA, followed closely by contrast-enhanced MRA and CTA.

Carotid Doppler Ultrasound

Carotid Doppler ultrasound is a safe imaging modality for the detection any stenosis in the carotids andand measuring blood velocities. Doppler measures that have been correlated with angiographic stenosis include

1.end-diastolic velocity

2.internal carotid artery peak

3.systolic velocity

4.ratios of internal carotid artery and common carotid artery peak systolic velocity.

CT Angiography

CTA is a sensitive, specific, and accurate technique for imaging the extracranial vessels and is superior to carotid ultrasound in differentiating a carotid occlusion from a very high-grade stenosis.

Conventional Angiography

DSA is the best imaging technique for cervical carotid and vertebral arteries, particularly when invasive therapies are considered.It can also provide information about collateral flow, perfusion status, and other occult vascular lesions that can affect patient treatment.

Perfusion CT and MRI

It has become paramount that the information about the nature and severity of the ischemic injury is as important as the "time" of the ischemic event for predicting outcome and prognosis and in making judicious therapeutic judgments.It is now stated that the ischemic salvageable "penumbral" tissue should be a target for reperfusion and neuroprotective strategies but requires proper patient selection. Brain perfusion imaging techniques provide information about regional cerebral hemodynamics in the form of cerebral blood volume, cerebral blood flow and mean transit time.. Perfusion imaging can very much indicate areas that are severely and irreversibly infarcted.Advantages of the CT over MRI include large scale availability of emergency CT imaging, quick imaging, and fewer contraindications to CT versus MRI. Disadvantages of the CT over MRI include the use of ionizing radiation and iodinated contrast which carries a risk of nephrotoxicity. Use of low-osmolar or iso-osmolar contrast minimizes this risk.Another disadvantage is limited brain coverage which is overcome by the latest 256- and 320-slice CT.

Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy is caused by gadolinium-based contrast agents and hence are generally avoided in the presence of advanced stages of renal failure with estimated glomerular filtration rate <30 $mL/min/m^2$.Arterial spin labeling can be used to negate the need of gadolinium

contrast material.

TREATMENT

Intravenous rtPA

Intravenous fibrinolytic therapy for acute stroke is the best treatment available.The Only FDA approved drug for intracranial fibrinolysis is reteplase.Reteplase is a recombinant form of human plasminogen activator which is non glycosylated .It has a longer half life than other tissue plasminogen activator due to its amino acid chain modification.Its half life is about 13 – 16 minutes.Since reteplase can easily penetrate inside the formed thrombus,it can produce an enhanced fibrinolytic activity,which will allow for rapid perfusion and decreased chances of bleeding.

[4]Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours

INCLUSION CRITERIA

Patient presenting with ischemic stroke

Presentation less than 3 hours from the time of onset of symptoms

Age greater than 18 years

EXCLUSION CRITERIA

History of head trauma or stroke within a period of 3 months

Symptoms suggestive of subarachnoid haemorrhage

Previous history of intracranial haemorrhage

Any history of intracranial aneurysm,neoplasm

Any recent history of intracranial or intraspinal surgery

High blood pressure greater than 185/110

Any active internal bleeding

Platelet less than 100000/mm3

Elevated a PTT due to heparin administration within 2 days

History of anticoagulant intake which raises INR greater than 1.7 or PT greater than 15 seconds

Random blood sugar less than 50mg/dl

CT brain which shows infarction greater than 1/3 rd cerebral hemisphere.

Patient taking direct thrombin inhibitors or direct factor Xa inhibitors with elevated aPTT,PT,TT etc

RELATIVE EXCLUSION CRITERIA

Pregnancy

History of seizures at the onset of stroke with post ictal residual symptoms.

Rapidly improving neurological symptoms

History of recent myocardial infarction within a period of 3 months

History of major trauma or surgery within a period of 14 days

History of recent urinary or gastrointestinal haemorrhage within a period of 3 weeks.

[4]Additional inclusion and exclusion characteristics of patients with acute ischemic stroke who could be treated with iv rtPA within 3-4.5 hrs from symptom onset

INCLUSION CRITERIA

Ischemic stroke presenting with neurological defecit

Patient presenting within 3 – 4.5 hours of symptom onset

RELATIVE EXCLUSION CRITERIA

Age greater than 80 years

NIHSS greater than 25 indicating severe stroke

History of oral anticoagulant intake

History of both prior stroke and diabetes

INTRAVENOUS rtPA

[4]STEPS FOR INFUSION OF RETEPLASE

1.0.9 g/kg to a maximum of 90 mg is infused over a period of 1 hour ,out of which 10% of this is given as loading dose over a period of 1 minute.

2.During the infusion, if the patient develops headache,hypertension,vomiting or if there is a worsening of neurological symptoms,the infusion is discontinued and an urgent CT SCAN is taken.

3.The patient is assessed for any neurological deterioration every fifteen minutes during and after infusion for a period of two hours,followed by every half an hour for six hours and then hourly until 24 hours after IV treatment. The blood pressure should be also be checked in this manner.

4.The frequency of blood pressure measurements should be increased if the blood pressure is above 180/105.If the blood pressure is high, anti-hypertensive medications should be administered.

5.CT / MRI scan should be taken 24 hours after reteplase infusion prior to starting anticoagulants or antiplatelets.

6.Insertion of catheters,nasogastric tubes should be delayed if the patient can be managed without these.

Anti-platelets

Oral Agents

Aspirin is the antiplatelet agent that has been used most widely and helps in the prevention of recurrent events.Aspirin is usually used in a dose of 75-325 mg daily and is associated with a 22% reduction of recurrent stroke[28].It is a irreversible cyclooxygenase inhibitor and usually starts acting within 2 hours. Clopidogrel or dipyridamole are not commonly used in the setting of acute stroke since treatment with clopidogrel with a daily dose of 75 mg produces maximum inhibition of platelet aggregation only after five days. This delay presents a problem for an early treatment effect in the management of patients with acute ischemic stroke.

NEUROPROTECTIVE AGENTS

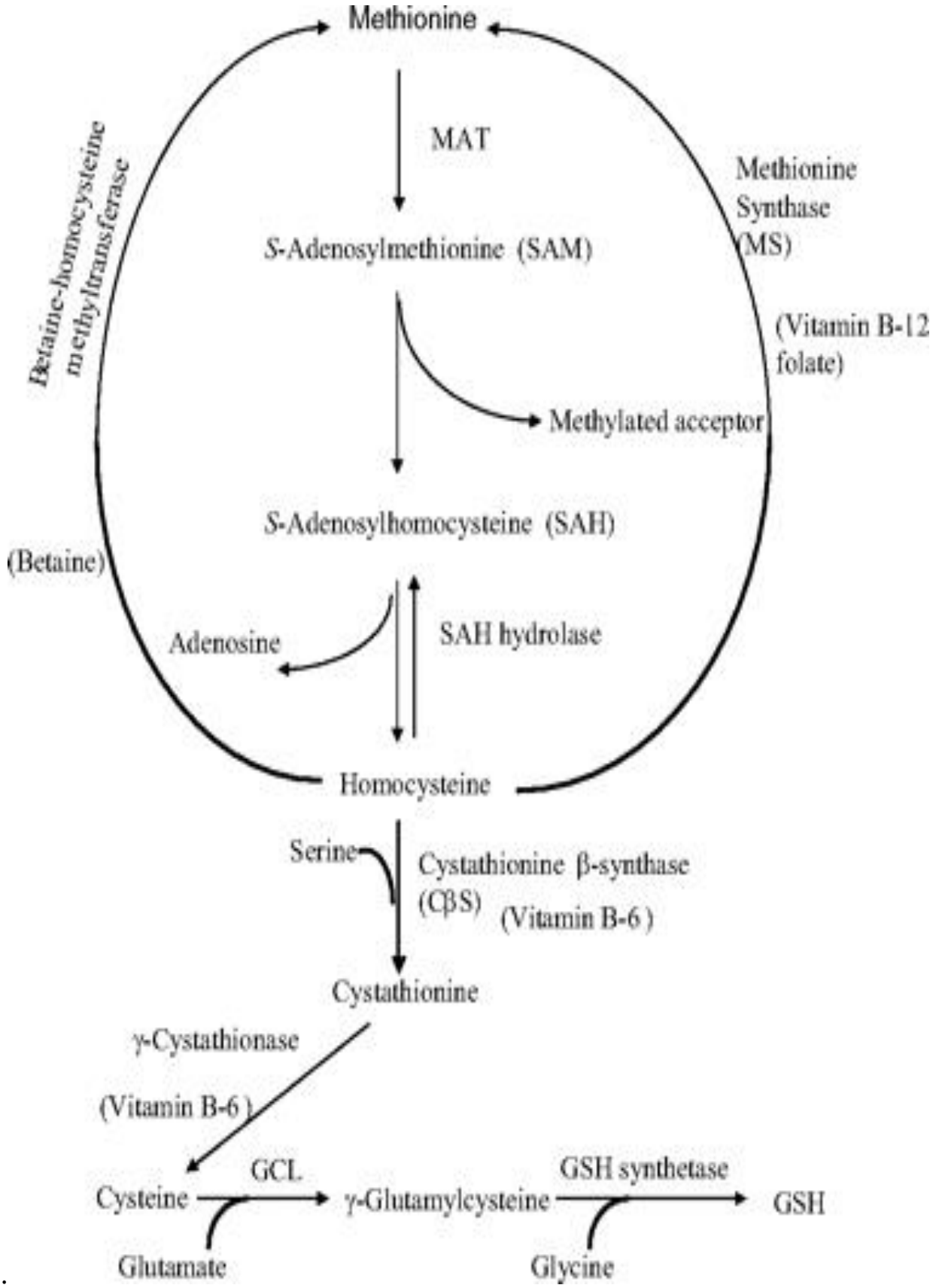
Neuroprotection is the technique of applying a therapy that directly affects the brain tissue to reclaim or delay the infarction of the viable ischemic penumbra,rather than reperfusing the tissue.There are are a number of pharmacological agents that restrict the cellular effects of acute ischemia or reperfusion and may limit neurological injury after stroke.[29]**Citicoline**, a phospholipid precursor that stabilizes the cell membranes is one of the most widely used neuroprotective agent.In addition to their LDL–lowering effects, **statins**, or HMG-CoA reductase inhibitors also exert neuroprotective properties such as favourable effects on endothelial function, cerebral blood flow, and inflammation.

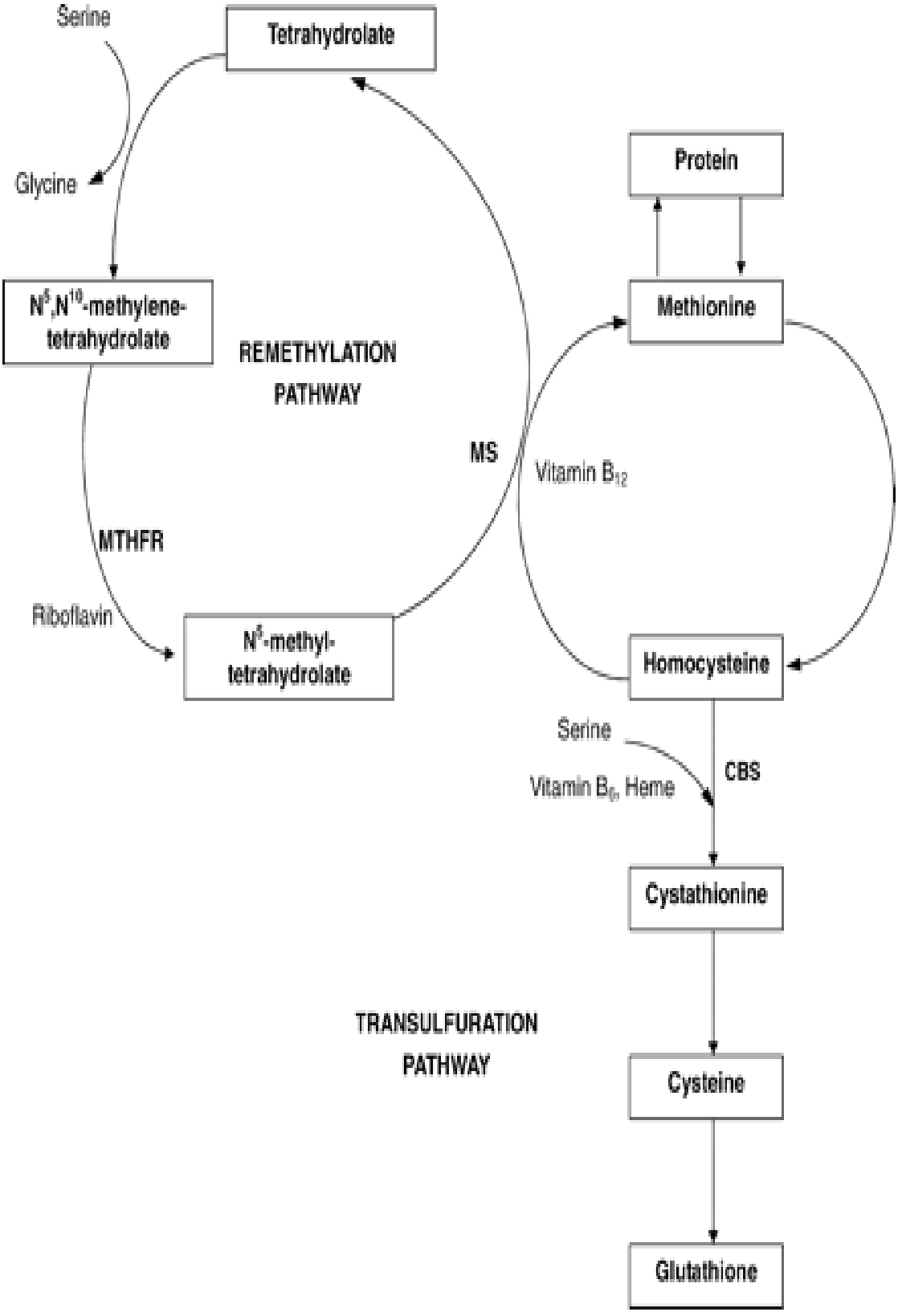
HOMOCYSTEINE AND STROKE

Homocysteine is a unique sulfur-containing amino acid which is necessary for one-carbon metabolism. It is the homologue of the amino acid cysteine, from which it differs by an additional methylene bridge (-CH_2-). It is synthesized from methionine by the removal of the terminal methyl group. Homocysteine can converted into methionine or cysteine.

HOMOCYSTEINE METABOLISM

[30]Homocysteine is not synthesized from the food we eat. Instead, it is synthesized from methionine via a complex process. Firstly, methionine receives an adenosine moiety from ATP, a reaction catalyzed by S-adenosyl-methionine synthetase, to give *S*-adenosyl methionine(SAM). SAM then transfers the methyl group to an acceptor molecule, (norepinephrine as an acceptor during epinephrine synthesis, DNA methyltransferase as an intermediate acceptor in the process of DNA methylation). The adenosine part is then hydrolyzed to yield L-homocysteine. L-Homocysteine has two primary fates: conversion via tetrahydrofolate (THFA) back into L-methionine or conversion to L-cysteine. Homocysteine is metabolized by any one of the two pathways: remethylation or transulfuration which is shown diagrammatically below[31].


Methionine
MAT
S-Adenosylmethionine (SAM)
Methionine Synthase (MS)
(Vitamin B-12 folate)
Betaine-homocysteine methyltransferase
Methylated acceptor
S-Adenosylhomocysteine (SAH)
(Betaine)
Adenosine
SAH hydrolase
Homocysteine
Serine
Cystathionine β-synthase (CβS)
(Vitamin B-6)
Cystathionine
γ-Cystathionase
(Vitamin B-6)
GCL
GSH synthetase
Cysteine
γ-Glutamylcysteine
GSH
Glutamate
Glycine


Serine
Tetrahydrolate
Glycine
Protein
N^5,N^{10}-methylene-tetrahydrolate
REMETHYLATION PATHWAY
Methionine
MS
Vitamin B_{12}
MTHFR
Riboflavin
N^5-methyl-tetrahydrolate
Homocysteine
Serine
Vitamin B_6, Heme
CBS
Cystathionine
TRANSULFURATION PATHWAY
Cysteine
Glutathione

LIFESTYLE AND PHYSIOLOGIC DETERMINANTS

Homocysteine level increases with age,and is higher in men and depends on renal function. Renal dysfunction raises plasma homocysteine levels by reducing homocysteine excretion . Homocysteine levels are also increased in male sex, smoking , high intake of coffee,sedentary lifestyle,alcohol consumption and old age.

Nutrition

Nutritional deficiencies in vitamin dependant cofactors which are required for homocysteine synthesis, such as folic acid, cyanocobalamin,riboflavin and pyridoxine can lead to hyperhomocysteinemia .

Genetic Determinants

A thermolabile variant of N^5,N^{10}-methylene-tetrahydroflolate reductase (MTHFR), caused by cytosine (C) to thymine (T) point mutation leads to substitution of valine for alanine[32] . This mutation reduces MTHFR activity by about 50%, which predisposes to hyperhomocysteinemia. Homozygosity for MTHFR C677T has been found in mainly Caucasian and Hispanic people.Cystathione β-synthase deficiency and MTHFR deficiency are the other determinants that will lead to hyperhomocysteinemia.

Other Associations

Hypothyroidism increases plasma homocysteine levels due to decreased renal function. Hyperhomocysteinemia has also been noted in

1.Rheumatoid arthritis [RA]

2.Psoriasis

3.Cancer, including breast, ovarian, and pancreatic cancer, and acute lymphoblastic leukemia [ALL].

The underlying mechanisms in in these conditions causing hyperhomocysteinemia are not clear.

Drugs[33]

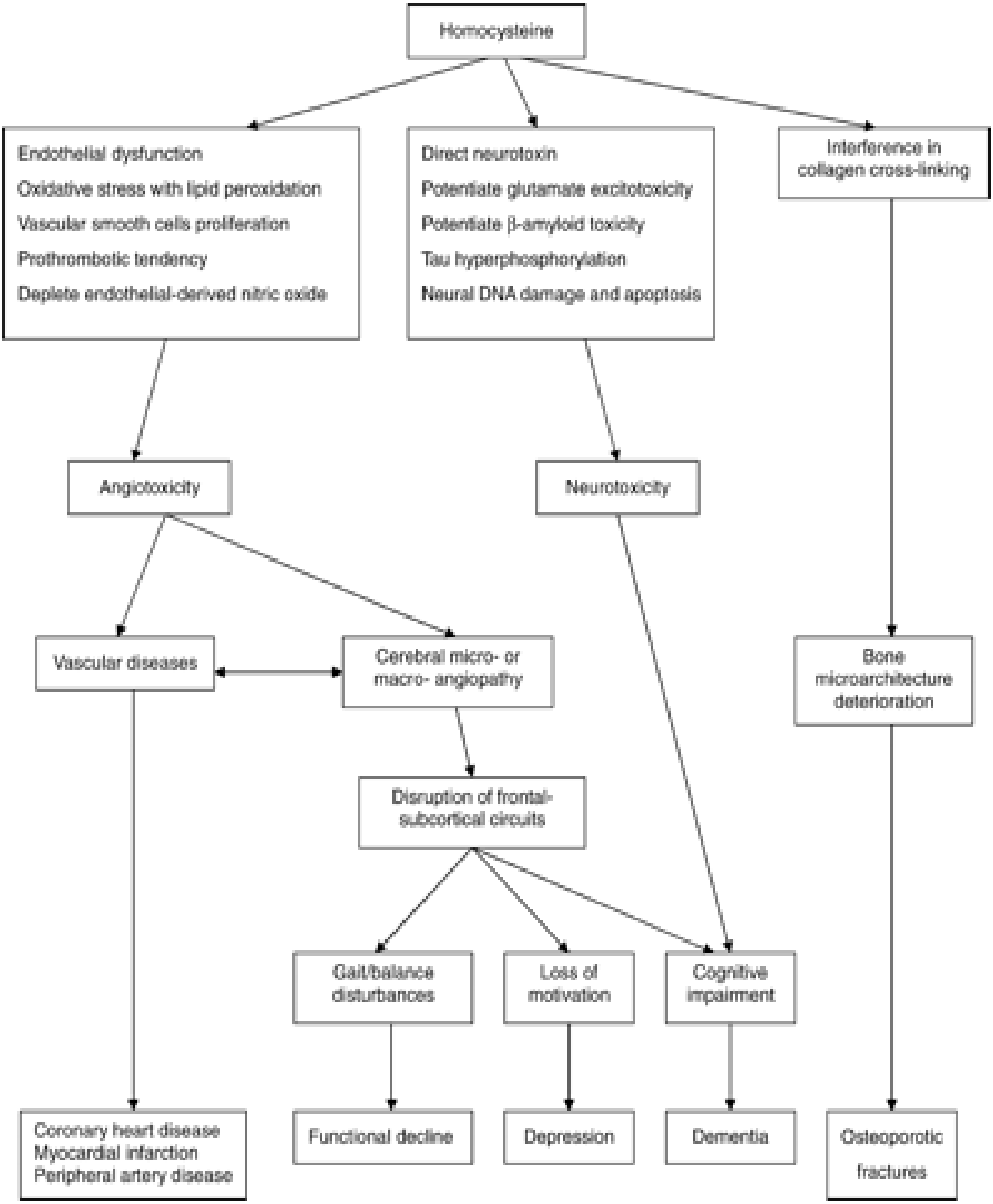
Main drugs causing hyperhomocystnemia are methotrexate ,phenytoin, carbamazepine, and valproic acid.Other drugs are theophylline, isoniazid, and hydralazine which act by inhibiting the synthesis of pyridoxine.

NORMAL HOMOCYSTEINE LEVEL[10]

The normal plasma level of homocysteine in the human body is 5–15 μmol/L. When the plasma homocysteine level >15 μmol/L there is hyperhomocystenemia and is classified as moderate (15–30 μmol/L), intermediate (30–100 μmol/L), and severe (>100 μmol/L). The prevalence of hyperhomocysteinemia is between 5% and 10%.

[9]HYPERHOMOCYSTENEMIA AND AGE RELATED PROBLEMS

The various systems affected by increased homocysteine levels and the proposed mechanisms responsible for these effects are summarized in the diagram which is shown below:


Homocysteine
Endothelial dysfunction
Oxidative stress with lipid peroxidation
Vascular smooth cells proliferation
Prothrombotic tendency
Deplete endothelial-derived nitric oxide
Direct neurotoxin
Potentiate glutamate excitotoxicity
Potentiate β-amyloid toxicity
Tau hyperphosphorylation
Neural DNA damage and apoptosis
Interference in collagen cross-linking
Angiotoxicity
Neurotoxicity
Vascular diseases
Cerebral micro- or macro- angiopathy
Bone microarchitecture deterioration
Disruption of frontal-subcortical circuits
Gait/balance disturbances
Loss of motivation
Cognitive impairment
Coronary heart disease
Myocardial infarction
Peripheral artery disease
Functional decline
Depression
Dementia
Osteoporotic fractures

Vascular Diseases

Hyperhomocysteinemia is an independent risk factor for coronary artery disease. Hyperhomocystenemia is a strong independent predictor of cardiac events and mortality and morbidity in patients with angiographically confirmed coronary artery disease. Hyperhomocysteinemia plays an important role in the development of cerebrovascular disease, cerebral small-vessel disease or leukoaraiosis and peripheral vascular disease.

CAD and MI

Hyperhomocysteinemia is associated with increased prevalence of coronary artery disease and is also associated with increased mortality and morbidity of cardiac patients.

Stroke

Hyperhomocysteinemia is associated with increased stroke prevalence, silent brain infarcts and cerebral white matter lesions (leukoaraiosis)[34] .Increased homocysteine levels is a strong predictor for cerebrovascular disease in normotensive men.New silent infarcts seems to be increased in persons with hyperhomocystenemia and without any previous infarcts.

Carotid artery disease and peripheral arterial disease

There is a significant association between elevated homocysteine levels and extracranial carotid artery disease.Hyperhomocysteinemia predisposes to lower ankle–brachial index leading to peripheral atherosclerosis.

[35]Pathophysiologic mechanisms of vascular disease in hyperhomocysteinemia

A number of mechanisms have been proposed for the development of vascular disease in patients with hyperhomocysteinemia.The targets of homocysteine are

1.endothelial cell

2.platelet

3.vascular smooth muscle cell

4.blood lipids

5.coagulation factors

6.nitric oxide.

Homocysteine-induced arteriosclerosis is first seen as endothelial injury leading to significant platelet activation and finally by thrombus formation. Homocysteine is auto-oxidized in plasma, leading to the formation of superoxide and hydrogen peroxide which causes endothelial damage and oxidative modification of low-density lipoprotein[LDL] , resulting in the

formation of foam cells. Homocysteine also promotes the proliferation of vascular smooth muscle cells by inducing cyclin A gene expression and hence greatly contributes to atherosclerosis.

Homocysteine also creates a prothrombotic environment by activating factor V, reducing protein C activation , inactivating the expression of thrombomodulin , inducing expression of tissue factors , suppressing the anticoagulant heparin sulfate expression , and blocking tissue plasminogen activator binding to endothelial cells. Finally, homocysteine depletes the endothelium-derived nitric oxide and reduces its production , further impairing the endothelial function.

[38]Cognitive Impairment

Alzheimer's disease and vascular dementia accounts for most of the cases of dementia in the old and homocysteine which can act as a neurotoxin may act as a causative factor.Alzheimers and vascular dementia patients were detected to have higher levels of homocysteine .Hyperhomocysteneimia can also affect the cognition psychomotor speed ,thinking and memory of the patients.

[37]Depression

The older population are very frequently associated with depression and hyperhomocysteinemia is found to be associated with depressive symptoms in old age.Depression itself can lead to anorexia and decreased food intake which and can lead to poor nutrition and vitamin deficiencies and thus lead to hyperhomocysteinemia.

[36]Osteoporotic Fracture

The main characteristics of osteoporosis are decreased bone mineral density, which affects the bone microstructure which predisposes to increased risk of fracture with more cases being reported in the elderly.Hyperhomocysteinemia is being noted in patients with osteoporosis.Hyperhomocysteinemia is also associated with increased with fractures since homocysteine distorts cross-linking of collagen , and thus can cause fractures.

[9]HOMOCYSTEINE LOWERING THERAPY

The therapeutic options for lowering elevated homocysteine are :

1.Folic acid

2.Vitamin B6

3. Vitamin B12

4. S-adenosyl-methionine

5. Zinc

6. Inositol

7. Choline

8. Trimethylglycine (TMG)

Folic acid (0.5 to 5 mg/day) decreases homocysteine levels by 25% in patients with high homocysteine levels. Vitamin B12 produces a small additional effect (7%), whereas vitamin B6 treatment alone only reduces post-methionine load. Betaine (trimethylglycine) reduces fasting homocysteine by 12 % to 20%.

METHODS AND MATERIALS:

This study was done at Government Royapettah Hospital, Chennai for a period of six months from Febraury 2015 to July 2015. The study was performed after procuring informed written consent from all the participants involved. Clearance was obtained from the Ethical Committee of the Government Kilpauk Medical College & Hospital Chennai.

STUDY DESIGN:

The study design is a case control study.

POPULATION:

Study group : Cases were patients admitted with acute ischemic stroke in ward and compared with controls

.

METHODOLOGY:

Patients admitted to medical ward with acute ischemic stroke clinic were assessed after obtaining written informed consent.Clinical data was obtained from the patient.Serum homocysteine levels,random blood sugar,serum cholesterol and blood pressure was measured in each patient and their controls and compared according to the different classes.

INCLUSION CRITERIA

1.Clinical evidence of stroke

2.Cranial computed tomography (CT) scan or MR imaging consistence with ischemic stroke

EXCLUSION CRITERIA

1. Patients with CT scan or MR imaging showing hemorrhage or mass lesion
2.Patients with previous history stroke
3.Patients with coronary artery disease
4.Patients with vasculitis
5.Patients with other liver and renal diseases
6.Patients with multiple risk factors
7.Patient taking multi vitamin tablets

DATA COLLECTION

The data of each patient was collected on a proforma specially designed for this study and which includes clinical features, past medical history and the presence of any risk factors. The clinical data obtained will be analysed for statistical significance and correlation.

SAMPLE SIZE

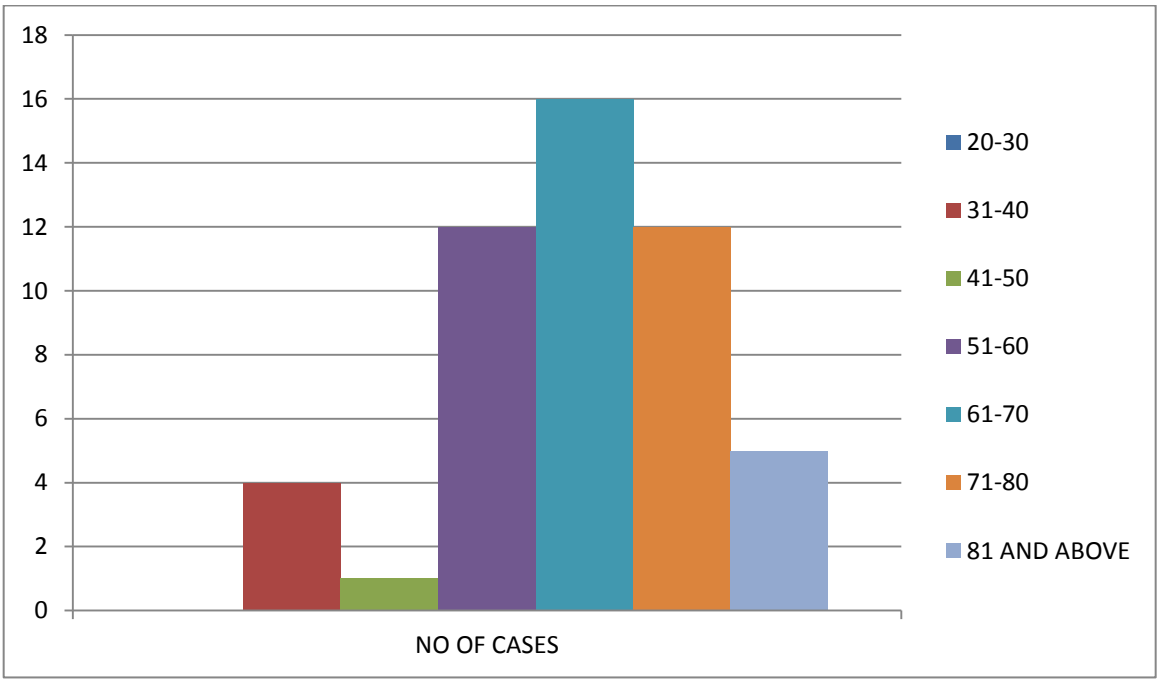
As per formula, sample size was calculated to be 50 case with 50 controls.

STATISTICAL ANALYSIS

STATISTICAL ANALYSIS

The statistical analysis was obtained using the SPSS software.

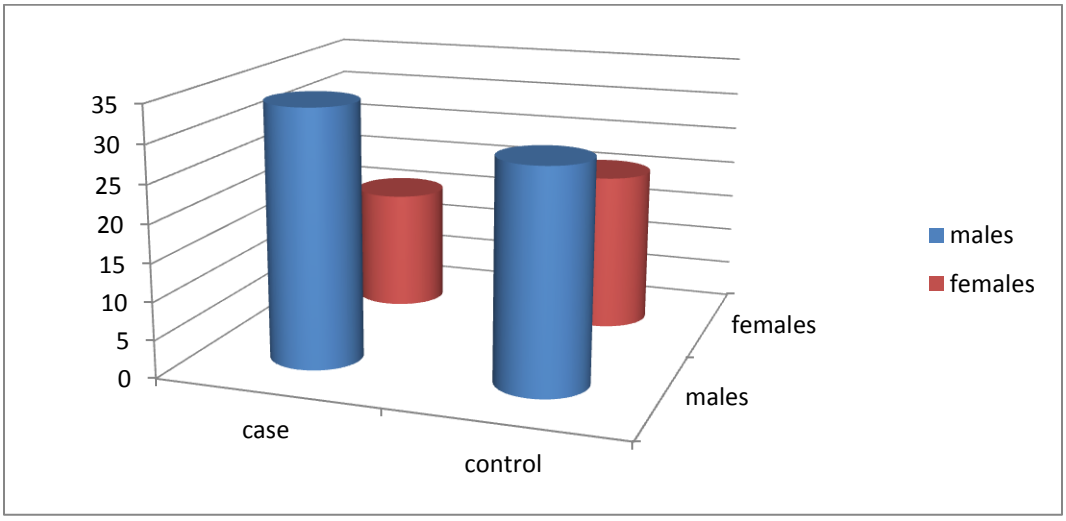
1. AGE DISTRIBUTION OF CASES



From the above graph,it is clear that most of the stroke cases was segregated in the middle of the graph.16 cases were seen in the 61 – 70 age group,12 cases in 51 -60 and 71-80 age group.5 cases were in the age group of 81 and above.Only 1case was seen in 41 -50 age group and 4 cases in 31- 40 age group.No cases were present in 20- 30 age group. Hence we can see that most of the cases are in the elderly age group.

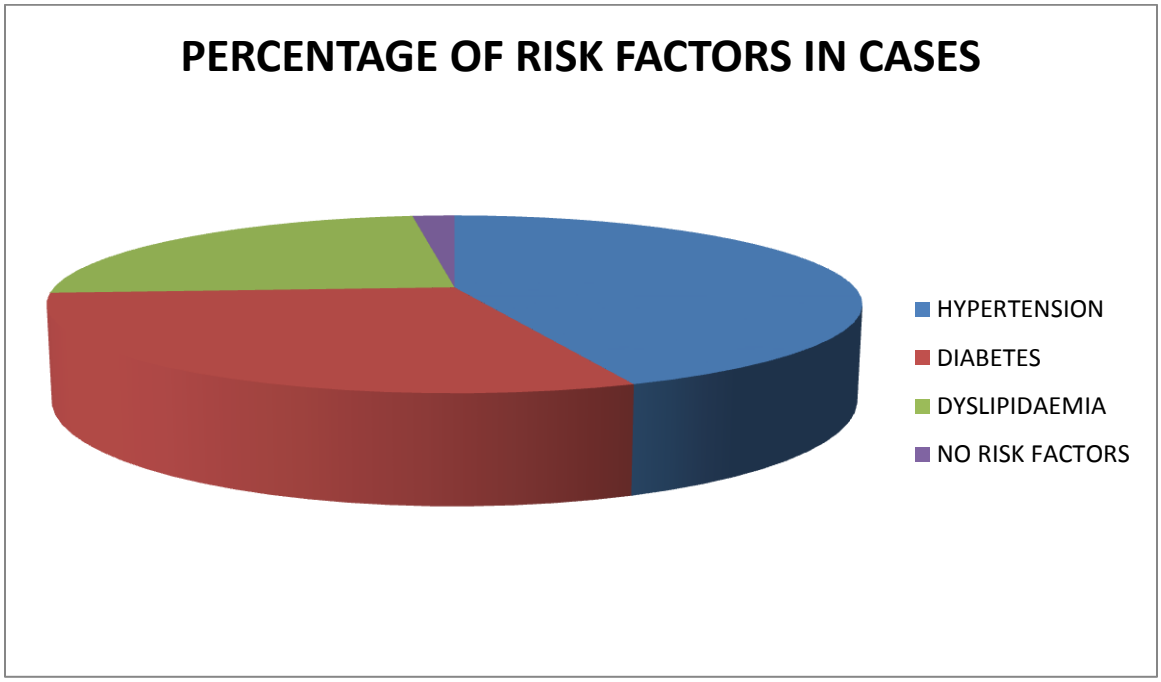
2.SEX DISTRIBUTION IN CASE AND CONTROL

Sex		Group		Total	P value
		Control	Cases		
Male	Count	29	34	63	0.300
	% within Sex	46.0%	54.0%	100.0%	
	% within Group	58.0%	68.0%	63.0%	
Female	Count	21	16	37	
	% within Sex	56.8%	43.2%	100.0%	
	% within Group	42.0%	32.0%	37.0%	
Total	Count	50	50	100	
	% within Sex	50.0%	50.0%	100.0%	
	% within Group	100.0%	100.0%	100.0%	



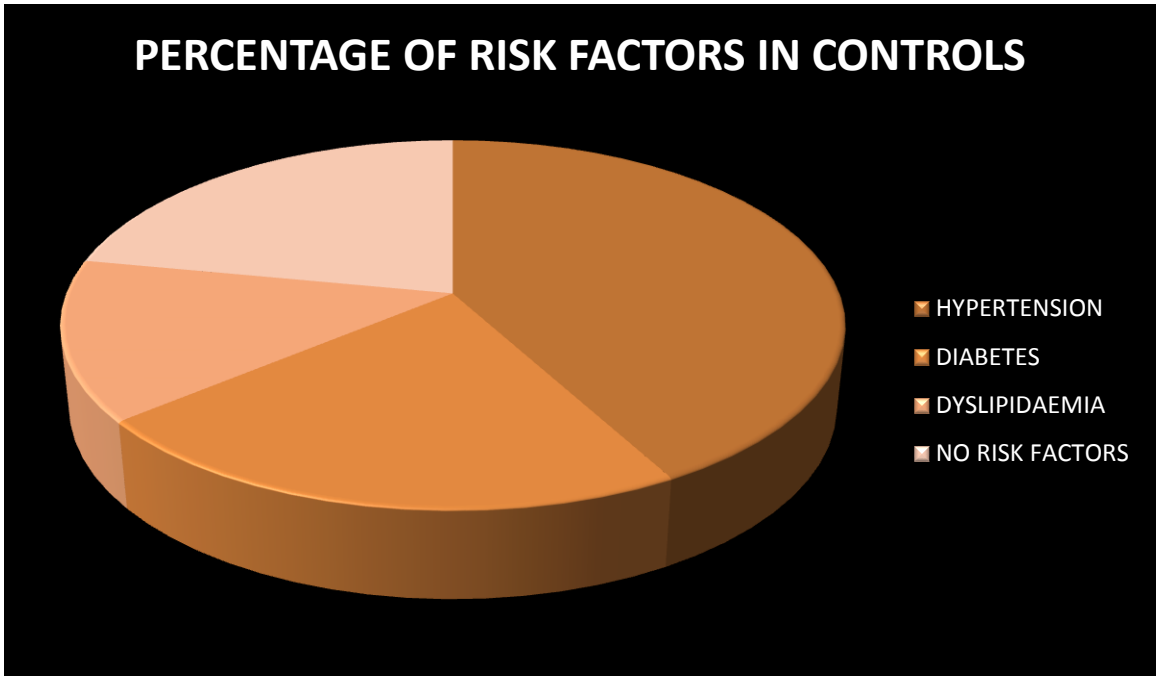
From the table and graph above ,it is inferred that males make up 68% of the case ie 34 of the 50 cases which confirms that ischemic stroke is more prevalent in the male population.

3.RISK FACTORS IN CASES



The above graph shows the percentage of risk factors contributing to ischemic stroke cases with hypertension being predominant ,present in about 22 cases (44%), diabetes in 15 cases (30%) and dyslipidaemia in 12 cases(24%).No risk factors were detected in 1 case(2%).

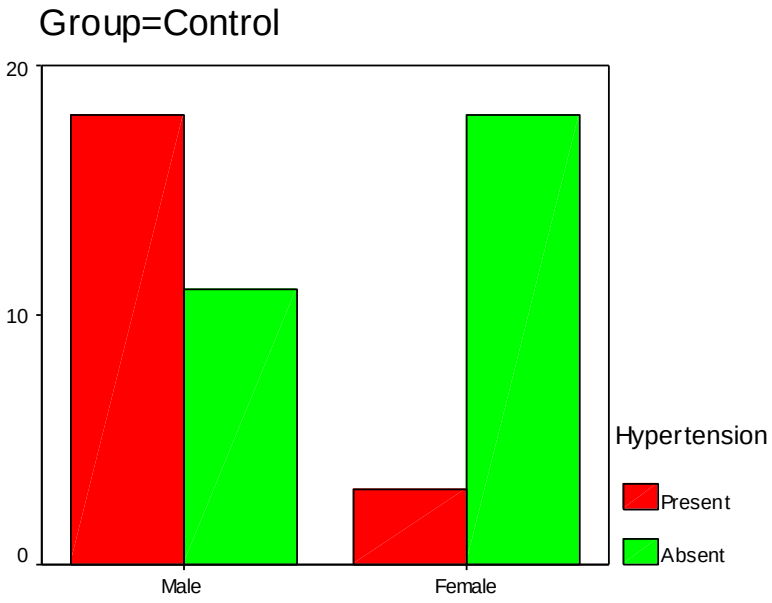
4.RISK FACTOR IN CONTROLS

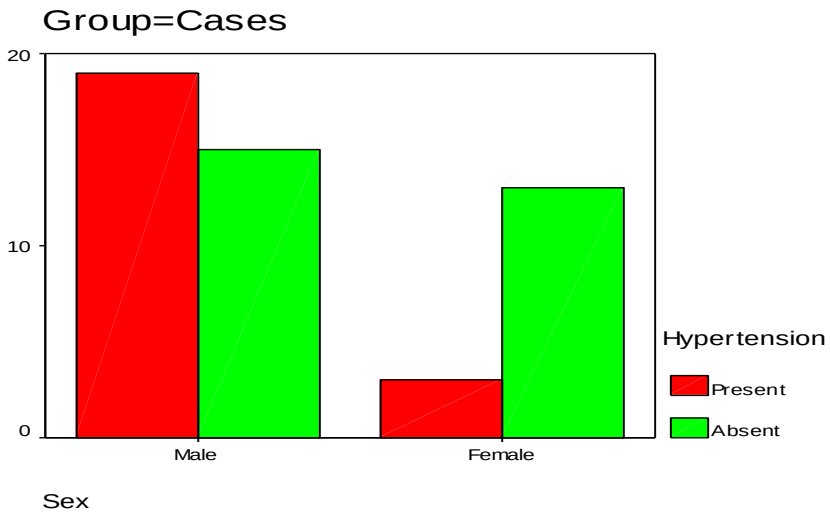


Among the control , hypertension contributes 21 cases(42%),diabetes 11 cases (22%),dyslipidaemia 7 cases(14%) and cases with no risk factors 11 in number(22%).

5.DISTRIBUTION OF RISK FACTORS REGARDING SEX

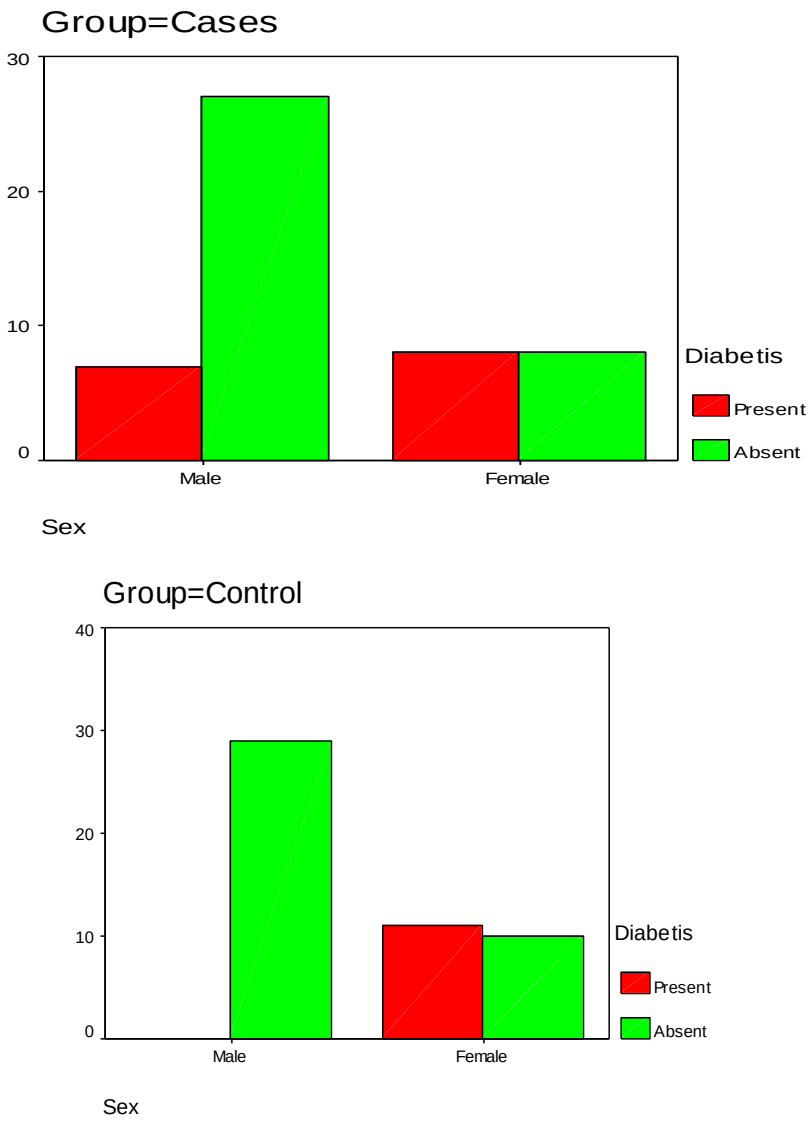
a)HYPERTENSION





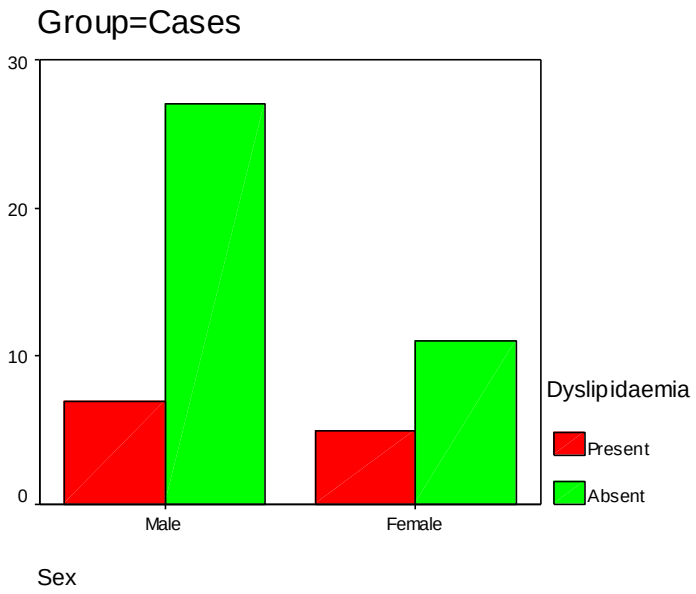
From the table above ,it seen that hypertension is present in 19 male cases and only 3 female cases and was present in 18 male controls and 3 female controls. Hence hypertension was more common in the males both cases and controls.

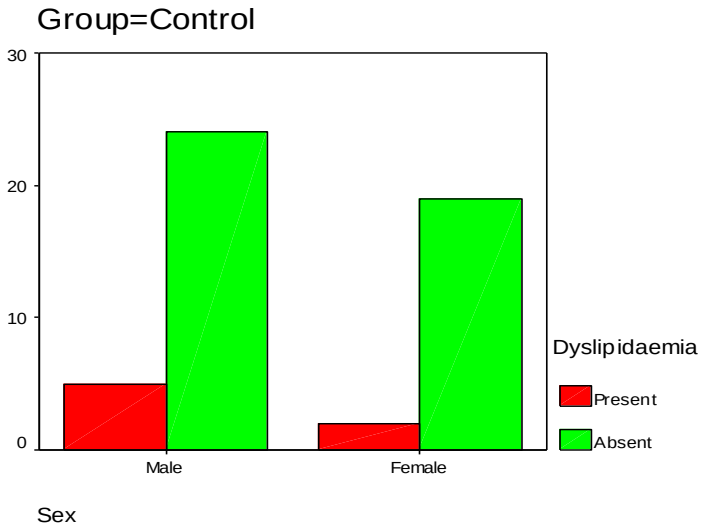
b)DIABETES



From the graphs above ,it is noticed that diabetes was present in 7 male case and 8 female cases ,but was absent in any male controls and present in11 female controls. Hence, it is observed that diabetes was observed more in the female population in the study sample.

c)DYSLIPIDAEMIA

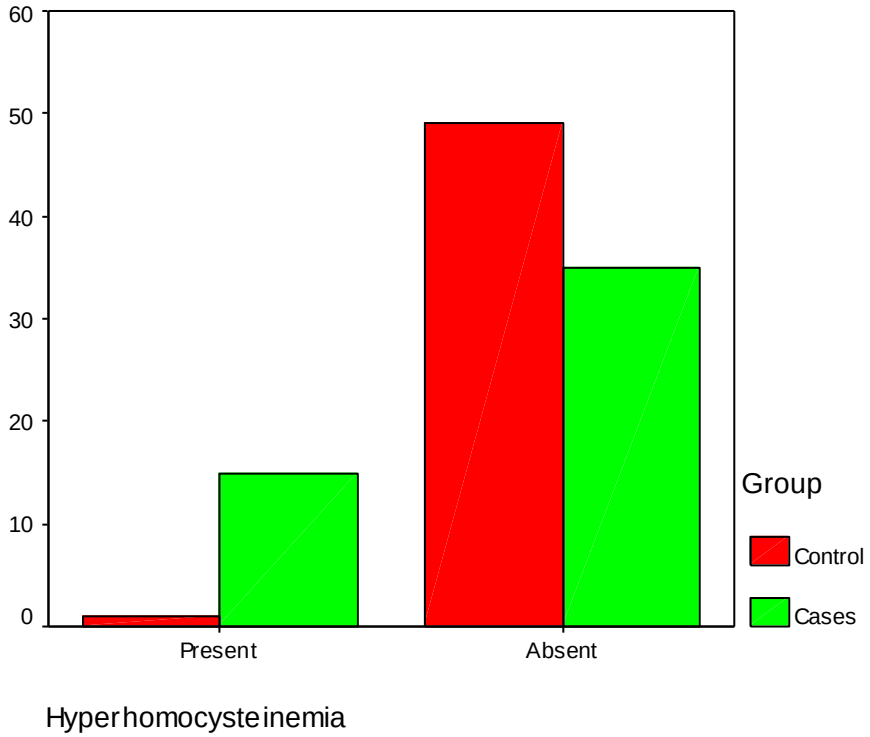




The above graphs shows that in the study dyslipidaemia was present in 7 males and 5 females among the cases and in 5 males and 2 females among the controls.This shows that dyslipidaemia was more common in the male population in the study group.

6.PRESENCE OF HYPERHOMOCYSTENEMIA

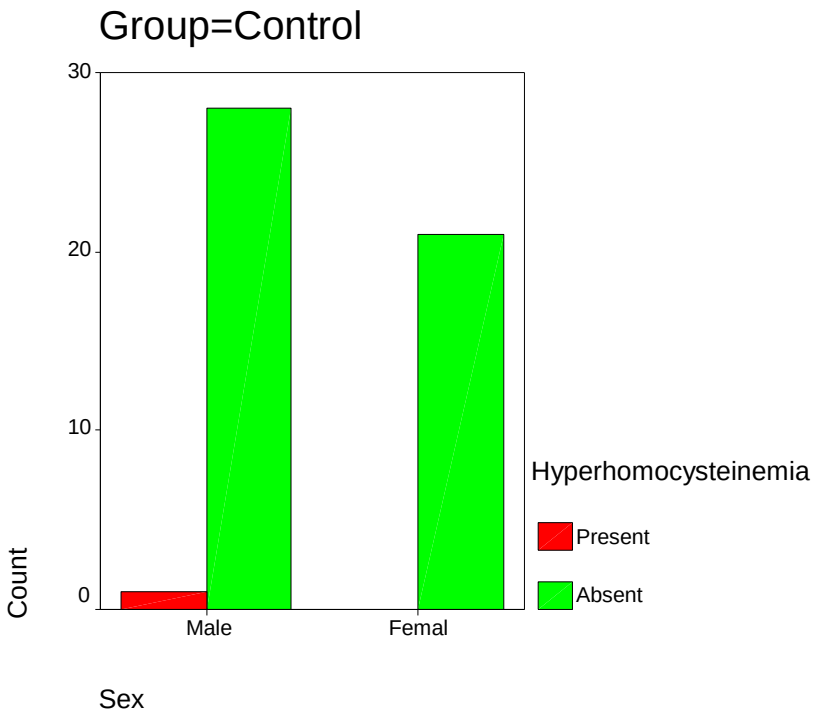
			Group		Total	P value
			Control	Cases		
Hyperhomocysteinemia	Present	Count	1	15	16	Less than 0.001**
		% within Hyperhomocysteinemia	6.3%	93.8%	100.0%	
		% within Group	2.0%	30.0%	16.0%	
	Absent	Count	49	35	84	
		% within Hyperhomocysteinemia	58.3%	41.7%	100.0%	
		% within Group	98.0%	70.0%	84.0%	
Total		Count	50	50	100	
		% within Hyperhomocysteinemia	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

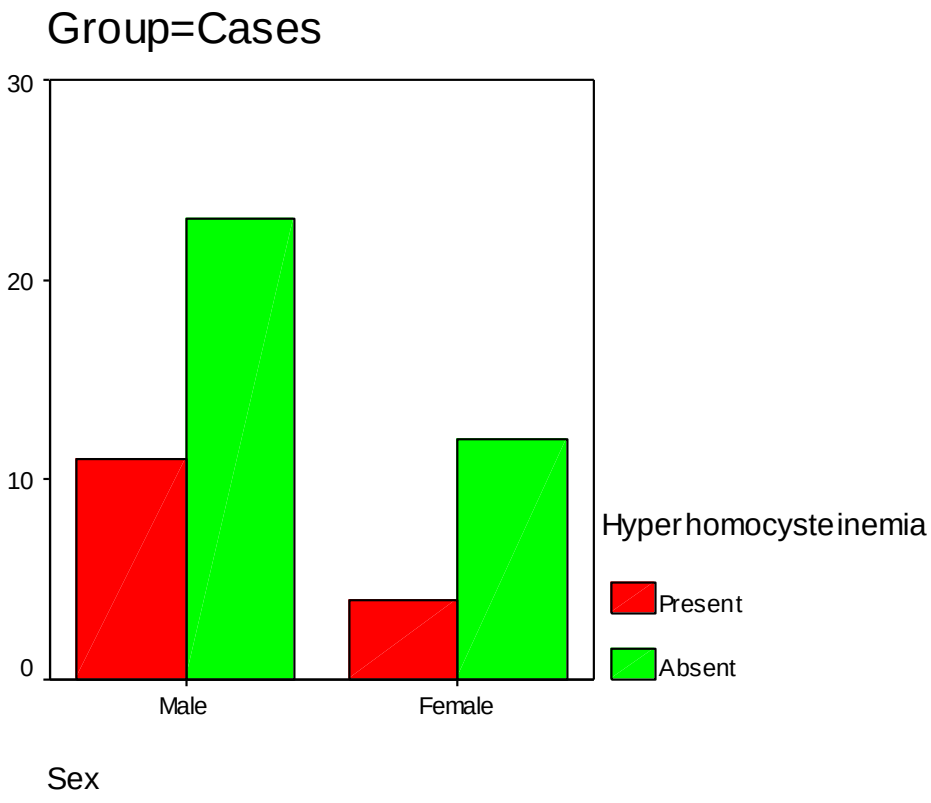


The above table shows the presence of hyperhomocystenemia in cases and controls.Hyperhomocystenemia is present in 30 % of the cases and only in 2 % of the controls and was absent in 70 % of the cases and 98% of the controls with significant statistical correlation and which shows the association of hyperhomocystenemia with stroke.

7.HYPERHOMOCYTEINEMIA AND SEX DISTRIBUTION

Group				Hyperhomocysteinemia		Total	P VALUE
				Present	Absent		
Control	Sex	Male	Count	1	28	29	0.300
			% within Sex	3.4%	96.6%	100.0%	
			% within Hyperhomocysteinemia	100.0%	57.1%	58.0%	
		Female	Count	0	21	21	
			% within Sex	.0%	100.0%	100.0%	
			% within Hyperhomocysteinemia	.0%	42.9%	42.0%	
Total			Count	1	49	50	
			% within Sex	2.0%	98.0%	100.0%	
			% within Hyperhomocysteinemia	100.0%	100.0%	100.0%	
Cases	Sex	Male	Count	11	23	34	
			% within Sex	32.4%	67.6%	100.0%	
			% within Hyperhomocysteinemia	73.3%	65.7%	68.0%	
		Female	Count	4	12	16	
			% within Sex	25.0%	75.0%	100.0%	
			% within Hyperhomocysteinemia	26.7%	34.3%	32.0%	
Total			Count	15	35	50	
			% within Sex	30.0%	70.0%	100.0%	
			% within Hyperhomocysteinemia	100.0%	100.0%	100.0%	


Group=Control
30
20
10
0
Count
Male
Femal
Sex
Hyperhomocysteinemia
Present
Absent


Group=Cases
30
20
10
0
Male
Female
Sex
Hyperhomocysteinemia
Present
Absent

From the above table and graph we can infer that though not statistically significant,hyperhomocysteinemia is present in 32.4% of the male cases and 25% of the female cases.

Males make up 73.3% of the hyperhomocysteinemia cases and females just 26.7% of the hyperhomocysteinemia cases.

In the controls,hyperhomocysteinemia is noted in 3.4 % of the male controls and absent in 96.6% while in the female controls,hyperhomocysteinemia is absent in all.

8.HOMOCYSTEINE LEVEL

A)CASES AND CONTROLS

	Group	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**P value**
Homocysteine Level	Control	50	7.36	1.871	.265	
	Cases	50	16.22	6.274	.887	0.001**

B)MALE CASE AND CONTROLS

	MALE	N	Mean	Std. Deviation	Std. Error Mean	P value
Homocysteine Level	Control	29	7.55	2.245	.417	
	Cases	34	16.82	6.626	1.136	0.001**

C)FEMALE CASE AND CONTROLS

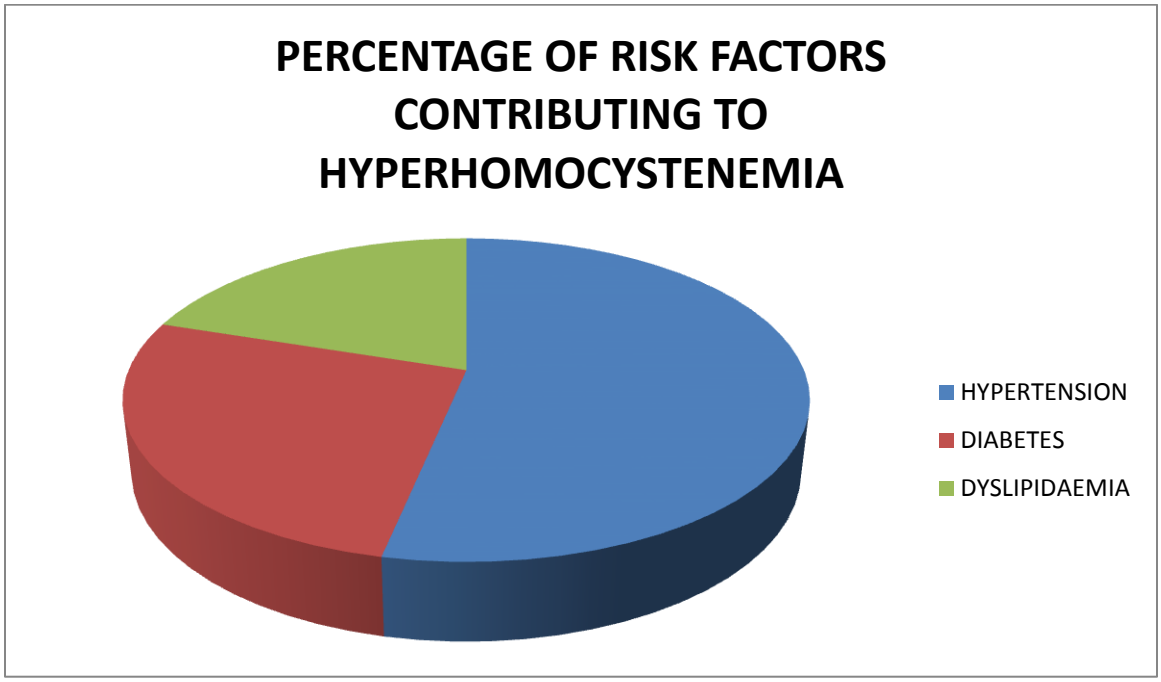
	FEMALES	N	Mean	Std. Deviation	Std. Error Mean	P value
Homocysteine Level	Control	21	7.10	1.179	.257	0.001**
	Cases	16	14.94	5.422	1.355	

D)ALL MALES AND FEMALES

	Sex (both case and controls)	N	Mean	Std. Deviation	Std. Error Mean	P value
Homocysteine Level	Male	63	12.56	6.881	.867	
	Female	37	10.49	5.342	.878	0.119

The mean homoysteine level in the cases is 16.32 and in the controls is 7.36 which is statistically significant with p value less than 0.05 which showed that that hyperhomocysteinemia is indeed a risk factor for stroke.Mean homocysteine value is 16.82 in male cases and 7.55 in male controls.The mean homocysteine value is 14.94 in female cases and 7.10 in female control which shows that homocysteine levels were significantly higher in male and female case than controls.Mean homocysteine levels were slightly higher in males than in females(both case and controls) but it was not statistically significant.

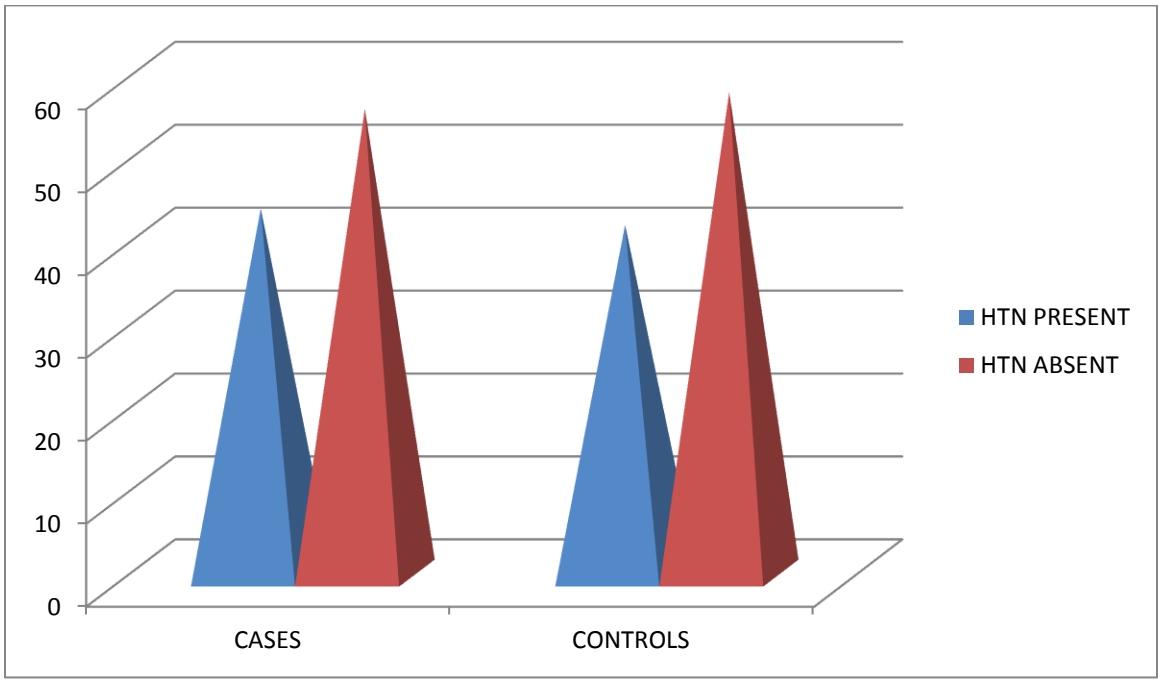
9.RISK FACTORS CONTRIBUTING TO HYPERHOMOCYSTENEMIA



From the above pie chart, it is clear that most of the hyperhomocystenemia cases were associated with hypertension (36.4%),followed by diabetes (26.7%),and finally dyslipidaemia(25%).1 case of hyperhomocystenemia had no history of hypertension,diabetes or dyslipidaemia.

A)HYPERTENSION GROUP COMPARISION

Hypertension			Group		Total	P value
			Control	Cases		
	Present	Count	21	22	43	
		% within Hypertension	48.8%	51.2%	100.0%	
		% within Group	42.0%	44.0%	43.0%	
	Absent	Count	29	28	57	0.840
		% within Hypertension	50.9%	49.1%	100.0%	
		% within Group	58.0%	56.0%	57.0%	
Total		Count	50	50	100	
		% within Hypertension	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

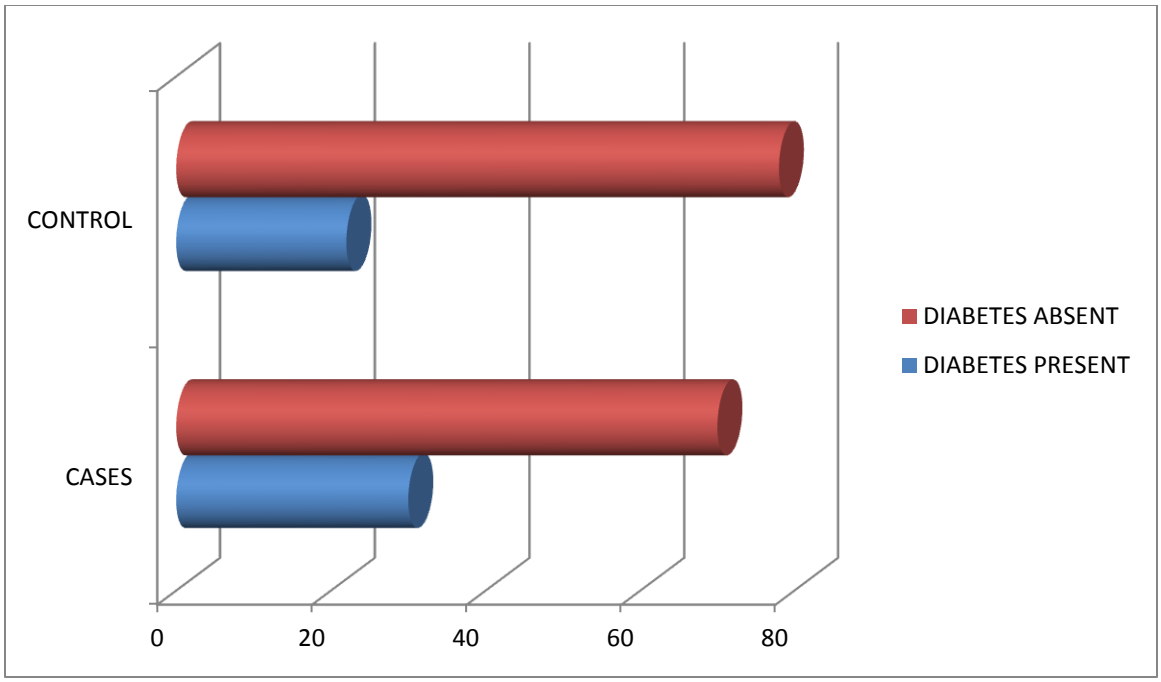


	Group	N	Mean	Std. Deviation	Std. Error Mean	P value
Homocysteine Level	Control	21	7.43	1.399	.305	0.001**
	Cases	22	17.82	6.877	1.466	

The above tables shows that hypertension is present in 44% and absent in 56% of the cases and present in 42% of the cases and absent in 58% of the controls.The mean value of homocysteine in hypertensive case and control is 17.82 and 7.43 respectively which shows that homocysteine is increased in hypertensive ischemic stroke patients.

B)DIABETES GROUP COMPARISION

			Group		Total	P value
			Control	Cases		
Diabetes	Present	Count	11	15	26	
		% within Diabetes	42.3%	57.7%	100.0%	
		% within Group	22.0%	30.0%	26.0%	0.362
	Absent	Count	39	35	74	
		% within Diabetes	52.7%	47.3%	100.0%	
		% within Group	78.0%	70.0%	74.0%	
Total		Count	50	50	100	
		% within Diabetes	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	

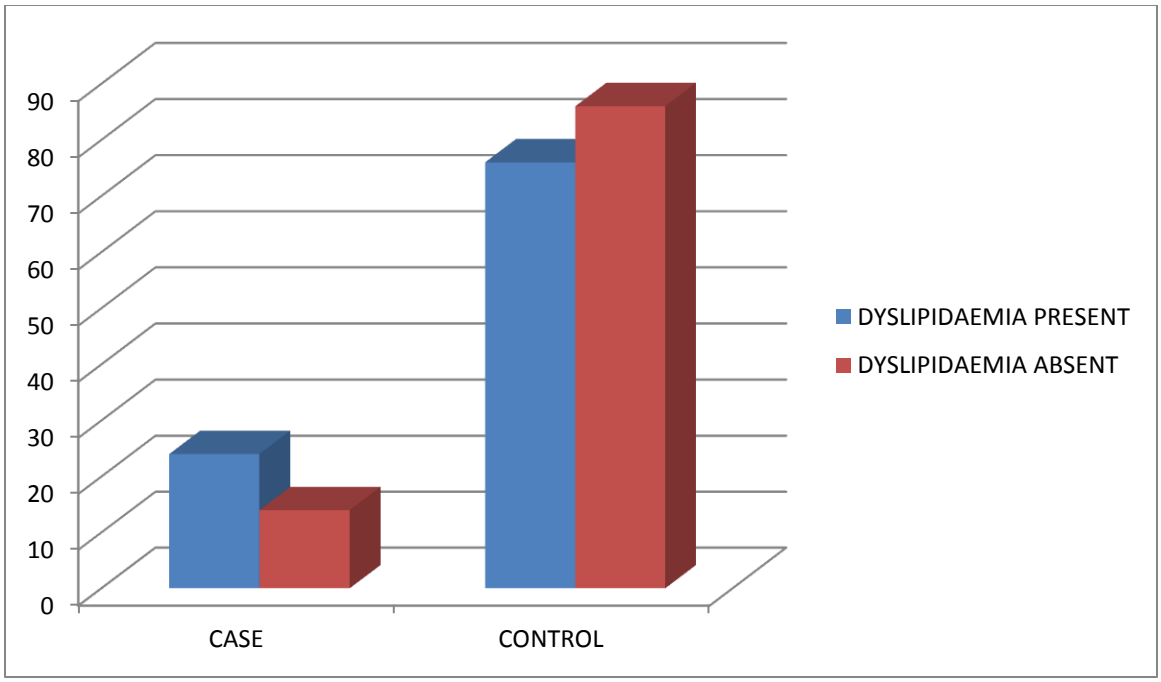


	Group	N	Mean	Std. Deviation	P VALUE
Homocysteine Level	Control	11	7.36	1.120	0.001**
	Cases	15	15.20	5.583	

From the above tables we can infer, that diabetes is present in 30% of the cases and absent in 70% of the cases and present in 22% of the controls and absent in 78% of the cases.The mean value of homocysteine in diabetic case is 15.20 and control is 7.36 which is statistically significant.

c)DYSLIPIDAEMIA GROUP COMPARISION

			Group		Total	P value
			Control	Cases		
Dyslipidaemia	Present	Count	7	12	19	0.202
		% within Dyslipidaemia	36.8%	63.2%	100.0%	
		% within Group	14.0%	24.0%	19.0%	
	Absent	Count	43	38	81	
		% within Dyslipidaemia	53.1%	46.9%	100.0%	
		% within Group	86.0%	76.0%	81.0%	
Total		Count	50	50	100	
		% within Dyslipidaemia	50.0%	50.0%	100.0%	
		% within Group	100.0%	100.0%	100.0%	



	Group	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
Homocysteine Level	Control	7	6.43	1.134	.429	
	Cases	12	14.92	5.946	1.716	0.001**

From the above graph and table it is clear that dyslipidaemia is present in 24 % and absent in 76% of the cases and present in 14 % and absent in 86% of the controls.The mean value of homocysteine level in case was 14.62 and controls was 6.43 which was statistically significant.

DISCUSSION

1.AGE DISTRIBUTION OF THE CASES

The mean age of the case is 65.46 with most of the cases clustered in the elderly age group.It was seen that most of the cases ie 16 cases were seen in the 61 – 70 age group,12 cases in 51 -60 and 71-80 age group each which shows that ischemic stroke usually occurs in the elderly population which is comparable with the study done by Tomassina et al[16] and according to the national stroke registry the crude prevalence rate of stroke in Indian is about 22 per 100000 persons[17].

2.SEX DISTRIBUTION IN CASES

68% of the ischemic stroke cases under study were males compared to females, which confirms that the male sex was at a higher risk to suffer from ischemic stroke which may be due to the fact that a higher percentage of male population will be having one or the other risk factors such as hypertension,diabetes, dyslipidemia, smoking or alcoholism.This was in concordance with the study done by Peter Appelros et al[15].

3.DISTRIBUTION OF RISK FACTORS WITH RESPECT TO SEX

Hypertension was found to be more common in the male population in this study compared to females and could be due to the smoking and alcoholic habits of the male population which by themselves increase the blood pressure and are independent risk factors for cardiac diseases.Diabetes was found to more common in female population in this study and dyslipidemia was found to be more common

in the male population according to this study.

4. HYPERHOMOCYSTENEMIA AND STROKE

It was seen that hyperhomocystenemia was present in 30% of the cases compared to 2% of the controls which is comparable to other studies such as Vekat[12] et al who found out 40% association in case and 4%in controls which indeed shows that hyperhomocystenemia is a risk factor for stroke.This was also comparable to other studies done by Orman et al and Eikelboom[11] et al.

The mean value of homocysteine in case was much higher in case than control(16.22 compared to 7.36) which further cements the stroke causative ability of elevated homocysteine and hence, we can find a strong correlation between homocysteine and ischemic stroke which is in concordance with Parnetti et al[13].

Most of the hyperhomocysteinemia cases were males(73.7%) compared to (27.3) in the females.The mean value among male cases was 16.82 and among females cases was 14.94 which although not statistically significant shows that hyperhomocysteinemia was more common in males which was in concordance with the study done by Carod-Artal et al[14].The mean homocysteine value is much higher in both male and female cases than controls.

Although this study found a strong correlation between hyperhomocystenemia and ischemic stroke,some studies have failed to do so.Another point to note is that there is no definite level of homocysteine above which there is drastic increase in vascular events,since some studies showed that stroke and other vascular compications can also occur within normal range of homocysteine levels.

5.HYPERHOMOCYSTEINEMIA AND RISK FACTORS

It was seen from the study that hypertension is present in 44% of the cases and the mean value of homocysteine in hypertensive case was 17.82, much higher than controls which shows that homocysteine is increased in hypertensive ischemic stroke patients. The strong association between hypertension and ischemic stroke was also seen by Carot-Artal et al[14].Hyperhomocysteinemia may lead to the loss of serine elastase which is very important for the maintenance of elasticity of the arterial wall and due to the loss of arterial elasticity and hence leads to hypertension.

The study shows that diabetes is present in 30% of the cases and the mean value of homocysteine in diabetic case is 15.20 and control is 7.36 which is statistically significant which is in concordance with Van Guldener et al[39], and also dyslipidemia is present in 24 % cases and and the mean value of homocysteine level in case was 14.62 and controls was 6.43 which was statistically significant which is in concordance with Xiaoyong et al[40].

CONCLUSION

1.Incidence of stroke is higher in the middle age and old age group. Most of the cases ie 16 cases were seen in the 61 – 70 age group,12 cases in 51 -60 and 71-80 age group each .

2.Incidence of stroke is higher in the male population but prevalence is higher in the female population due to their longevity.68% of the stroke cases were male patients, which showed the higher incidence of stroke in male population.

3.The homocysteine level was higher in the stroke cases compared to the controls which shows that homocysteine is a risk factor for ischemic stroke.The mean homocysteine level was 16.22 compared to7.36 in the controls.

4.Homocysteine level is higher in male cases than female cases.Mean homocysteine levels in males was 16.82 and in females was14.94

5.A number of risk factors are associated with increased homocysteine level.Hyperhomocysteinemia is asscociated in stroke cases with hypertension, diabetes,dyslipidiaemia.Among the risk factors,hypertension was more common male cases and controls than females,diabetes was common in the female cases and controls and dyslipidaemia was more common in male cases and controls than females

Hyperhomocystenemia is a risk factor for ischemic stroke especially in the younger age which is usually not associated with any risk factors.A large number of the younger population should be screened for their homocysteine levels and if found to be high, adequate supplementation of vitamin b12 and folate should be given. Also homocysteine levels are determined by genetics,pharmacology,nutrition and pathology the homocystein levels of the Indian population are very different compared to the western population and large number of large scale trials are needed to determine the homocysteine status of the Indian population

LIMITATIONS OF THE STUDY

1.Small number of cases and controls

2.Cases and controls with multiple risk factors were excluded

3.Levels of vitamin b12 and folate level were not measured in the patients since their deficiency can itself lead to hyperhomocystenemia.

4.Homocysteine levels were measured after stroke so it was not able to ascertain whether homocysteine was the cause of stroke or whether it was a consequence of stroke.

5.Smoking and alcoholism as a risk factor was not taken into account.

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Joseph Varon, MD

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ANNEXURES

PROFORMA

PERSONAL DETAILS

NAME

AGE

SEX

ADDRESS

PHONE NO.

EDUCATION

OCCUPATION

MONTHLY INCOME

DISEASE DETAILS

DISEASE DURATION

CO MORBITIES – DIABETES

HYPERTENSION

DYLIPIDAEMIA

SERUM HOMOCYSTEIN LEVEL

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10

Protocol ID. No.3/02/2015 Dt:01/02/2015

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "Hyperhomocysteianemia as a risk factor for ischemic stroke"- For Project Work submitted by Dr.Kiran Josy Kanjamala, Post Graduate in MD (GM)., Govt. Kilpauk medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

27/3/15

CHAIRMAN,
Ethical Committee
Govt. Kilpauk Medical College, Chennai

27/3/15

HYPERHOMOCYSTEINEMIA IN ACUTE ISCHEMIC STROKE

Dissertation submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of regulations

For award of the degree of

M.D (GENERAL MEDICINE)

BRANCH – I

KILPAUK MEDICAL COLLEGE

	A	B	C	D	E	F	G	H	I
1	name	case /control	age	sex	diabetis	hypertension	dyslipidaemia	HOMOCYSTEINE LEVEL	HYPERHOMOCYSTEINEMIA
2	SARASWATHY	CASE	81	F	+	-	- -	25	+
3	SELVAM	CASE	67	M	- -	-	- -	12	-
4	JANAKIAMMA	CASE	74	F	-	- -	+	14	-
5	PANDIAN	CASE	38	M	- -	+	-	28	+
6	bhaskar	CASE	57	M	+	-	- -	14	-
7	PARVATHHY	CASE	77	F	-	-	+	13	-
8	MOHAMMED	CASE	58	M	-	+	-	14	-
9	SHANTHA	CASE	68	F	+	-	-	13	-
10	SIVANRAJ	CASE	69	M	-	+	- -	29	+
11	PAULSWAMY	CASE	69	M	-	-	+	27	+
12	SAVITHRIAMMA	CASE	82	F	+	-	-	24	+
13	RENUKA DEVI	CASE	57	F	-	-	+	14	-
14	SHANKAR	CASE	37	M	-	+	-	21	+
15	FARISHA	CASE	78	F	-	+	-	10	-
16	SAMEUEL	CASE	67	M	+	-	-	13	-
17	BHARGAVI	CASE	59	F	-	+	-	13	-
18	SAMSUN	CASE	46	M	+	-	-	11	-
19	PALNIAPPA	CAES	78	M	-	-	+	10	-
20	PARTHIBAN	CASE	60	M	-	+	-	31	+
21	SHANTHI	CASE	72	F	+	-	-	26	+
22	SETHUPATHY	CASE	58	M	-	-	+	13	-
23	MOHANAKRISHNAN	CAES	65	M	-	-	+	19	+
24	PARASURAM	CASE	70	M	-	+	-	25	+
25	BHAGYAMMAL	CASE	59	F	+	-	-	19	+
26	SETHURAMAN	CAES	63	M	+	-	-	16	-
27	SUBRAMANIAM	CASE	64	M	-	+	-	28	+
28	PAVITHRAN	CASE	38	M	-	+	-	26	+
29	PALSAMY	CASE	68	M	+	-	-	12	-
30	SIVASUBRAN	CASE	54	M	-	-	+	26	+
31	SUBHADRAMMMA	CASE	76	F	+	-	-	12	-
32	IYYAMUTHU	CASE	81	M	-	-	+	11	-
33	RAJENDRAN	CASE	73	M	-	+	-	13	-
34	DURGAMMA	CASE	69	F	+	-	-	12	-
35	DEVI MEENAL	CAES	81	F	+	-	-	10	-
36	SETHUPATHY	CASE	76	M	-	+	-	14	-
37	MAHIVARNAN	CASE	69	M	-	+	-	14	-

	A	B	C	D	E	F	G	H	I
38	BHOOPATHY	CASE	59	M	-	+	-	13	-
39	ZEENATH BEEGUM	CASE	78	F	-	-	+	11	-
40	SUNDRAMAN	CASE	74	M	-	+	-	13	-
41	PATTAMMMAL	CASE	81	F	-	+	-	12	-
42	VINAYAGAM	CASE	63	M	-	+	-	13	-
43	SAVITHRI	CASE	54	F	-	-	+	11	-
44	RAHUTALLAH	CASE	79	M	+	-	-	10	-
45	SEKAR	CASE	59	M	-	+	-	14	-
46	MARIMITHU	CASE	38	M	-	+	-	13	-
47	DEVI PRASAD	CAES	65	M	-	-	+	10	-
48	MURUGESAN	CASE	63	M	-	+	-	14	-
49	LOGANATHAN	CASE	58	M	+	-	-	11	-
50	RAJA	CASE	66	M	-	+	-	22	+
51	DURAI	CASE	78	M	-	+	-	12	-
52	PRASANNAN	CONTROL	68	M	-	+	-	5	-
53	SELVAKUMAR	CONTROL	58	M	-	-	+	6	-
54	JANAKIAMMMA	CONTROL	74	F	+	-	-	7	-
55	VELAYUDHAM	CONTROL	78	M	-	+	-	8	-
56	BALRAJ	CONTROL	57	M	-	+	-	9	-
57	MEENAKSHIAMMA	CONTROL	79	F	+	-	-	8	-
58	DHANANJAYAN	CONTROL	68	M	-	-	+	8	-
59	MEHARUNISSA	CONTROL	79	F	+	-	-	9	-
60	AJAY	CONTROL	38	M	-	+	-	9	-
61	SHALINI	CONTROL	35	F	+	-	-	6	-
62	BALABHASKAR	CONTROL	67	M	-	+	-	8	-
63	JAI GANESH	CONTROL	58	M	-	+	-	8	-
64	SULOCHANA	CONTROL	76	F	-	-	+	5	-
65	JAI KUMAR	CONTROL	62	M	-	+	-	6	-
66	MARGARET	CONTROL	59	F	+	-	-	7	-
67	SYAM	CONTROL	34	M	-	-	-	6	-
68	MOHANAPRIYA	CONTROL	28	F	-	-	-	5	-
69	VISWABHARAM	CONTROL	71	M	-	+	-	5	-
70	LAKSHMIAMMA	CONTROL	67	F	+	-	-	8	-
71	DURGAMMA	CONTROL	75	F	-	-	+	6	-
72	SNEHALATHA	CONTROL	85	F	-	+	-	7	-
73	VISHAWANATHAN	CONTROL	59	M	-	+	-	7	-
74	MOHIT	CONTROL	36	M	-	-	-	17	+

75	RAHMAN	CONTROL	47	M	-	+	-	7	-
76	SELVAGANESH	CONTROL	26	M	-	-	-	6	-
77	SUBRAN	CONTROL	67	M	-	+	-	7	-
78	JAYASREE	CONTROL	46	F	+	-	-	6	-
79	GANESSAN	CONTROL	46	M	-	+	-	8	-
80	PATTAYAMAL	CONTROL	76	F	+	-	-	8	-
81	SREE GOVINDAN	CONTROL	47	M	-	+	-	7	-
82	SETTU	CONTROL	29	M	-	-	-	6	-
83	MANIMEHGHALAY	CONTROL	25	F	-	-	-	8	-
84	MUNISAMY	CONTROL	77	M	-	+	-	6	-
85	MUTHUKUMAR	CONTROL	69	M	-	-	+	6	-
86	KARTHICK	CONTROL	46	M	-	+	-	8	-
87	VADIVEL	CONTROL	56	M	-	-	+	8	-
88	IQBAL	CONTROL	37	M	-	-	-	8	-
89	VENDAL	CONTROL	64	F	+	-	-	6	-
90	MAHIMA	CONTROL	33	F	-	-	-	8	-
91	RAJA M	CONTROL	49	M	-	+	-	8	-
92	HEMALATHA	CONTROL	27	F	-	-	-	7	-
93	SELAV MANI	CONTROL	55	M	-	-	+	6	-
94	ABDUL REHMAN	CONTROL	60	M	-	+	-	11	-
95	VIJAYLAKSHMI	CONTROL	53	F	+	-	-	9	-
96	PADMAVATHI	CONTROL	48	F	-	+	-	6	-
97	REVATHY	CONTROL	29	F	-	-	-	8	-
98	SALMATH BEEGUM	CONTROL	50	F	+	-	-	7	-
99	SIVAM	CONTROL	26	M	-	-	-	7	-
100	AADILAKSHMI	CONTROL	65	F	-	+	-	8	-